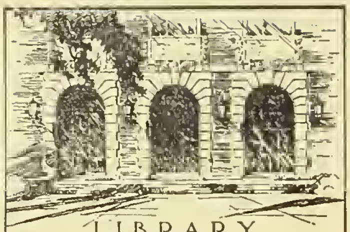

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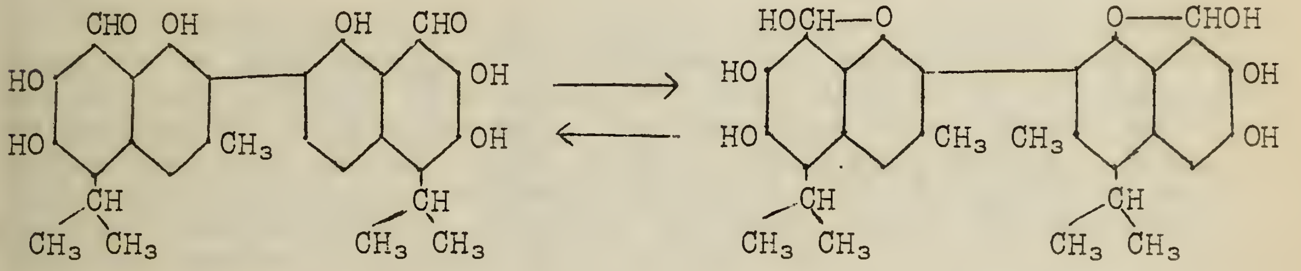
STRUCTURE OF GOSSYPOL

Adams et al. -- University of Illinois

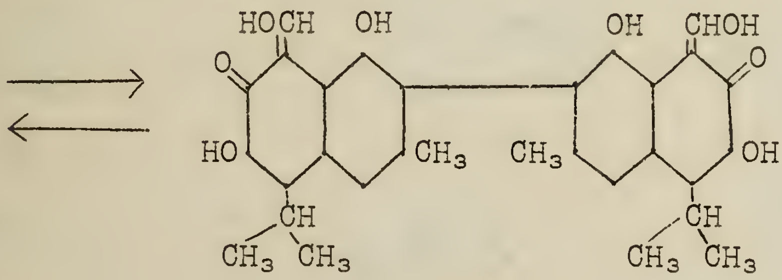
Gossypol, $C_{30}H_{30}O_8$, is the toxic principle and the yellow coloring matter in cottonseed. The structure has been deduced primarily through the study of the following reactions: (1) Color reactions which indicate two *ortho* hydroxyls and a keto group in a naphthalene nucleus, (2) formation of a dianilino or diamino derivative during which process two molecules of water are eliminated, (3) conversion of gossypol to anhydrogossypol by elimination of two molecules of water, (4) the formation of hexaacyl or hexaalkyl derivatives and their oxidative degradation products, (5) the loss of two CO groups from gossypol by the action of alkali to give apogossypol and the degradation of apogossypol hexamethyl ether, (6) the conversion of apogossypol hexamethyl ether by action of cold sulfuric acid to desapogossypol hexamethyl ether which has C_6H_{12} less than the original molecule.

The assigned structure is 2,2-bi-1,6,7-trihydroxy-3-methyl-5-isopropyl-8-aldehydonaphthyl and exists in three tautomeric forms shown in Ia, Ib, and Ic.



Ia

Ib



Ic

Half molecules will be used to present the various derivatives since the original molecule is postulated as symmetrical as deduced from the even number of reagents which always react. The OCH_3 groups will be written as OR and the isopropyl as R.

The dianilino derivative is represented by IIa, IIb, and IIc.

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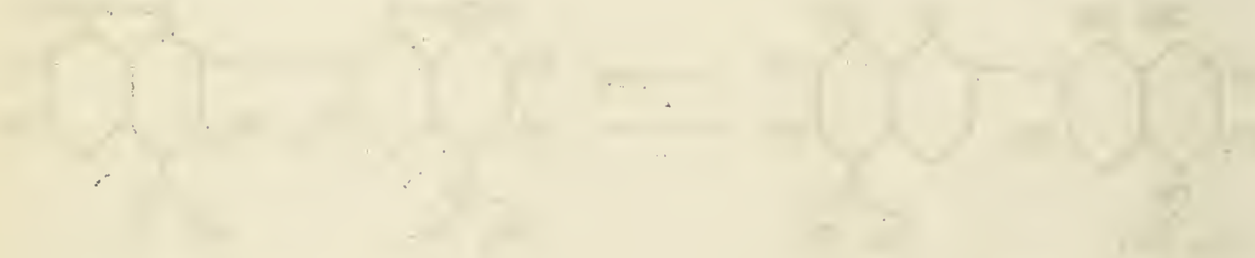
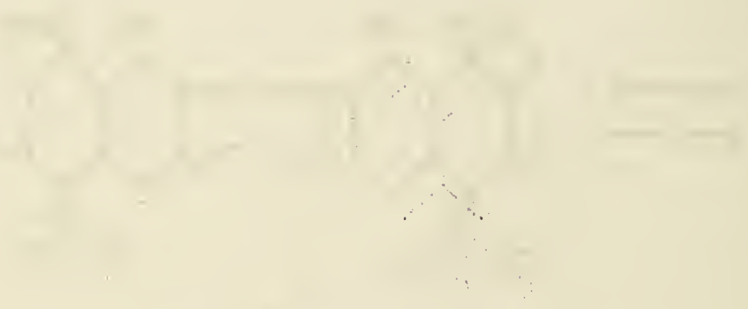
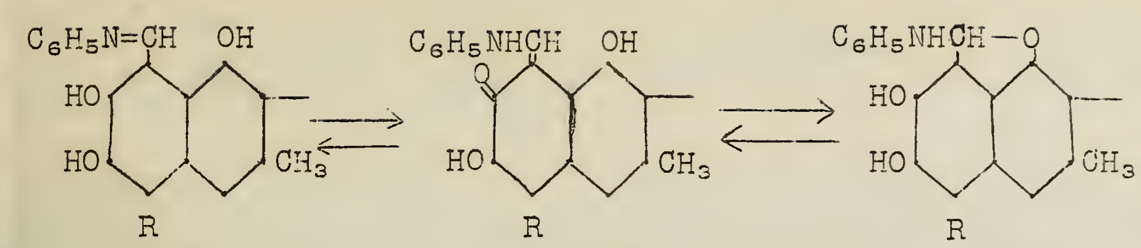
[illegible]

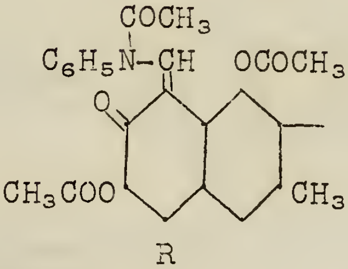
[illegible]







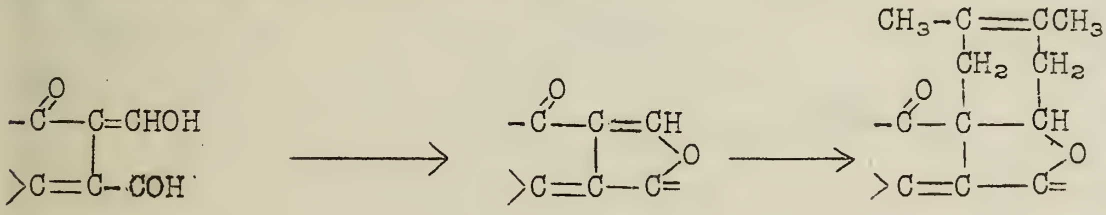
IIa IIb IIc



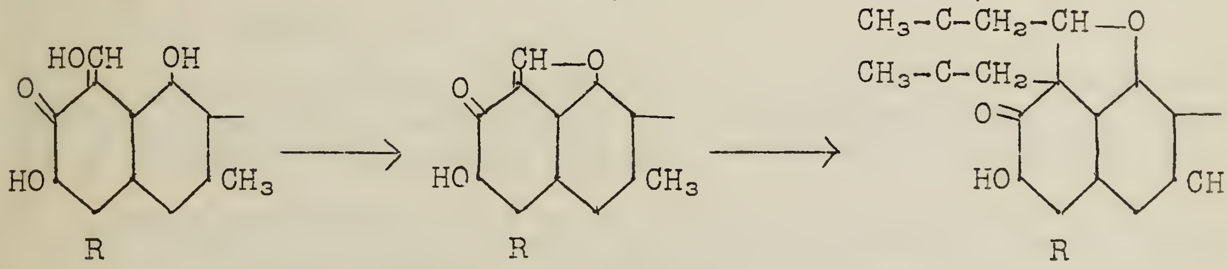
III

The acetate of II has an acetyl attached to nitrogen as shown by pyrolysis to acetanilide so that III may be the proper structure.

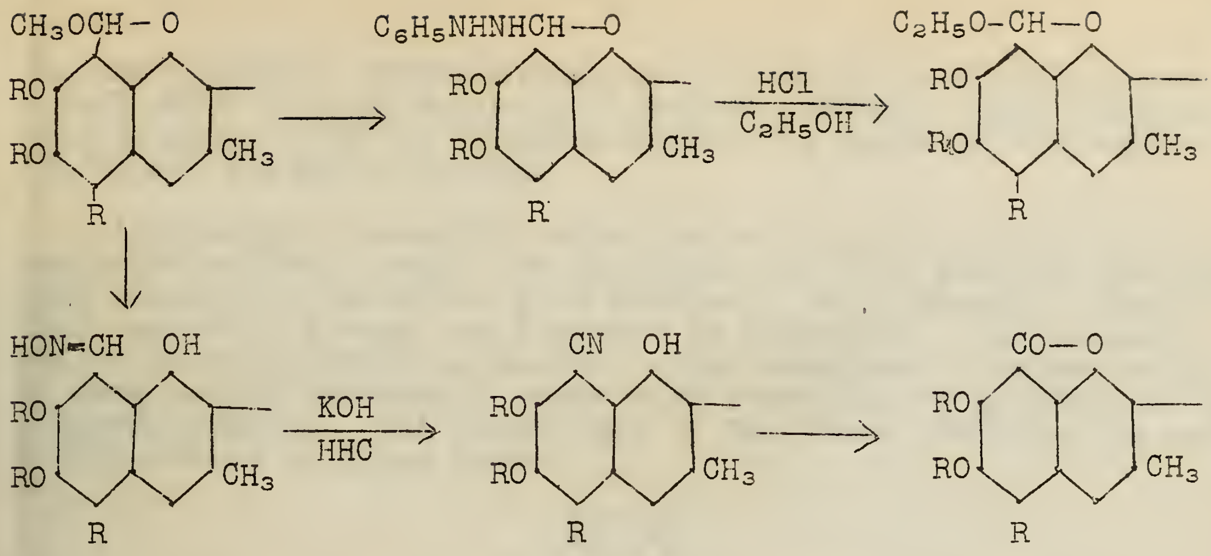
The anhydrogossypol adds ammonia, acetic anhydride and other reagents to give gossypol derivatives, from which it is deduced an easily-opened oxygen ring which is easily cleaved by reagents, must be present in anhydrogossypol. On the other hand, dienes add to anhydrogossypol and an oxygen ring is still left intact. These facts are explained by assuming the nuclei IV, V, and VI to be present respectively in gossypol, anhydrogossypol and the diene addition product resulting in V, VI and VII.



IV V VI

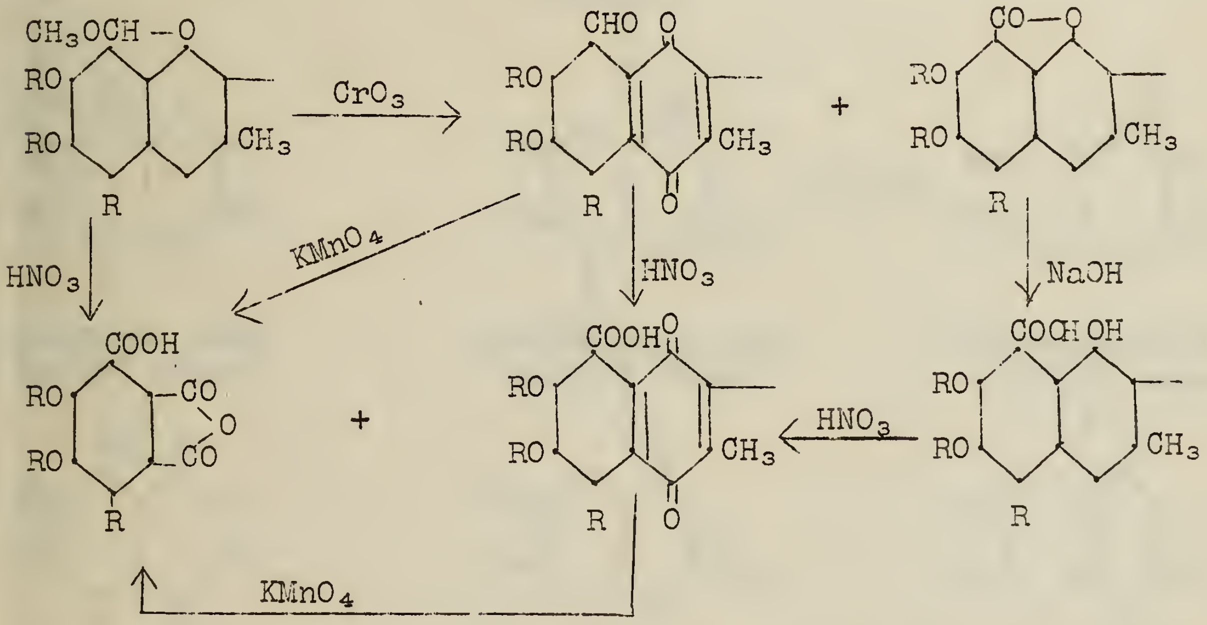


The hexamethyl ether of gossypol is a stable compound as compared with gossypol. It reacts with phenylhydrazine or hydroxylamine in acetic acid solution. Two methoxyls are first hydrolyzed and then the two aldehyde groups react. Two acetal methoxyls in the hexamethyl ether are assumed. Some of the more important transformations of these products are shown below.


CH3OCH—O
RO
RO
CH3
R
C6H5NHNHCH—O
HCl
C2H5OH
C2H5O-CH—O
HON=CH OH
KOH
HHC
CN OH
CO—O

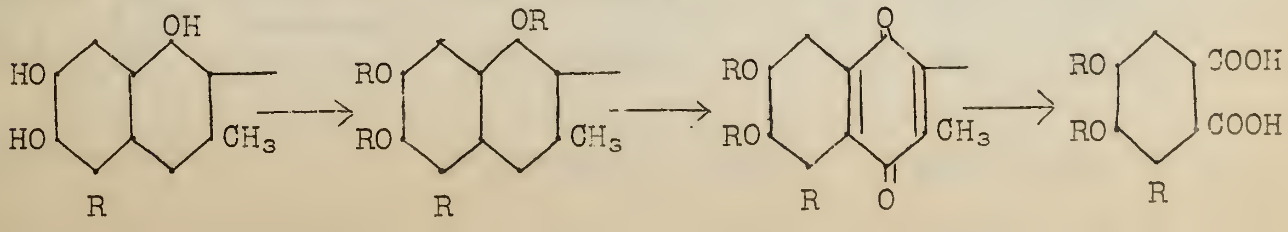
The last product shows all the characteristic reactions of a phenolic acid lactone.

The oxidative degradation of gossypol hexamethyl ether is shown below.


CH3OCH—O
RO
RO
CH3
R
CrO3
CHO O
O
+
CO—O
HNO3
KMnO4
HNO3
NaOH
COOH
CO
O
CO
COOH O
COOH OH
HNO3
KMnO4

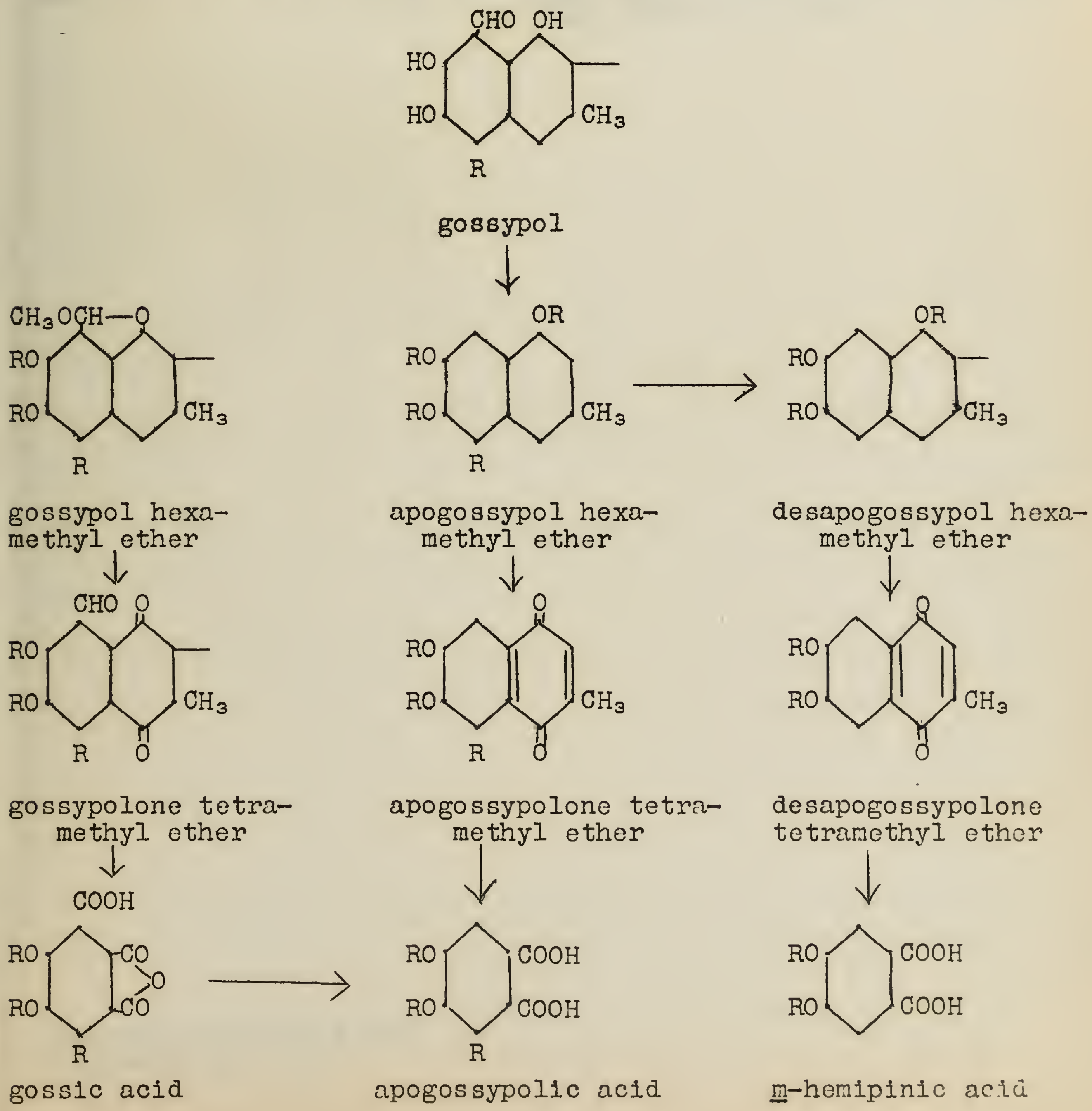
The benzene derivative, gossic acid, has all the reactions expected of such a molecule, methylation to a monomethyl ester, hydrolysis to a tribasic acid, demethylation to a dihydroxy compound, etc.

Hydroxyaldehydes lose a carbon and oxygen atom as formic acid by the action of alkali. Consequently apogossypol may be represented below with its degradation products.


OH
HO
HO
CH3
R
OR
RO
RO
O
COOH
COOH

The last product, apogossypolic acid, could be synthesized from gossic acid by elimination of a carboxyl group. Other reactions of apogossypolic acid are characteristic of a molecule containing the functional groups indicated.

Apogossypol hexamethyl ether loses C_6H_{12} by the action of concentrated sulfuric acid. No methoxyls are lost and the sulfuric acid liquors on oxidation give acetone. It is assumed, therefore, that isopropyl groups are replaced by hydrogens. The product called desapogossypol hexamethyl ether undergoes similar reactions to apogossypol hexamethyl ether with formation of m-hemipinic acid, a known compound. The comparison of the three degradations omitting intermediates is given below.


CHO OH
HO
HO
CH3
R
gossypol
CH3OCH—O
RO
RO
CH3
R
gossypol hexamethyl ether
OR
RO
RO
CH3
R
apogossypol hexamethyl ether
OR
RO
RO
CH3
desapogossypol hexamethyl ether
CHO O
RO
RO
CH3
R O
gossypolone tetramethyl ether
O
RO
RO
CH3
R O
apogossypolone tetramethyl ether
O
RO
RO
CH3
O
desapogossypolone tetramethyl ether
COOH
RO
RO
CO
O
CO
R
gossic acid
RO
RO
COOH
COOH
R
apogossypolic acid
RO
RO
COOH
COOH
m-hemipinic acid

The structure of the part of the gossypol connecting the naphthalene nuclei is assumed on the basis of analogy to other natural products and to the fact that gossypol by limited oxidation in the cold gives acetic acid.

Confirmatory evidence for the postulated structure of gossypol must await the synthesis of several degradation products.

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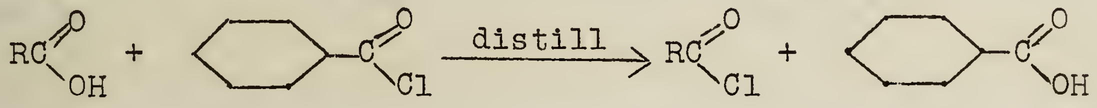
Adams et al., J. Am. Chem. Soc., 59, 1723, 1729, 1731, 1736 (1937
60, 2158-2204 (1938)

Reported by Roger Adams
September 21, 1938

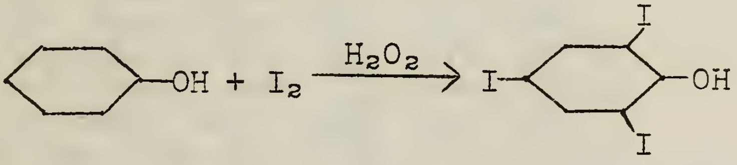
SOME NEW SYNTHETIC METHODS

Brown -- University of Chicago
Kumler -- University of California
Newman -- Ohio State University
Coles -- Mellon Institute

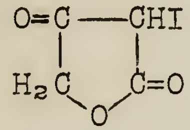
I. The Preparation of Volatile Acid Chlorides.--In the preparation of the higher acid chlorides thionyl chloride has found wide application and the chlorides of phosphorous are still useful. However with the lower, more volatile acids, the yields with thionyl chloride are not particularly satisfactory. Likewise the separation of the lower acid chlorides from phosphorous oxychloride is often very difficult. Brown has found the following method will give yields of from 80 to 92 per cent in the case of most of the lower acid chlorides:



II. The Preparation of α-Iodoenols.--Since the following reaction goes practically quantitatively:

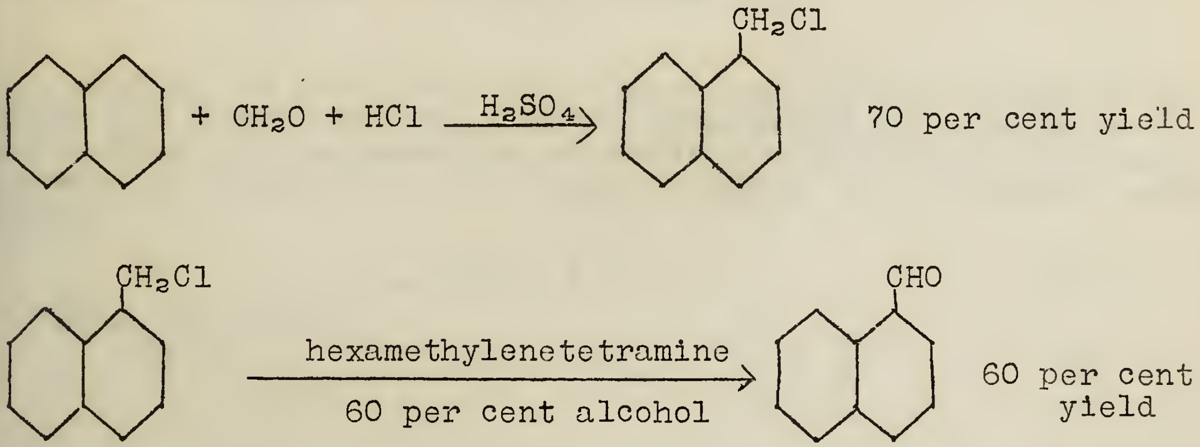


Kumler thought the method could be extended to aliphatic enols. On applying the same general procedure, he obtained the following results.

$CH_3COCHICOOC_2H_5$	90 per cent yield
$CH_3COCHICOCH_3$	80 per cent yield
	95 per cent yield

III. The Preparation of α-Naphthonitrile.--The Rosenmund-v. Braun nitrile synthesis has recently been modified and applied with great success in several instances, the most noteworthy of which is perhaps Newman's synthesis of α-naphthonitrile. By heating an α-halogenated naphthalene with cuprous cyanide in pyridine he obtained α-naphthonitrile in 93 per cent yield from α-bromonaphthalene and in 92 per cent yield from α-chloronaphthalene.

IV. The Preparation of α-Naphthaldehyde.--When Coles needed to prepare α-naphthaldehyde on a large scale, he found the standard methods either too expensive or lengthy to be feasible. However, he was able to adapt an older and little used procedure to suit his purposes. It is outlined below.


+ CH_2O + HCl
H_2SO_4
CH_2Cl
70 per cent yield
CH_2Cl
hexamethylenetetramine
60 per cent alcohol
CHO
60 per cent yield

Bibliography:

I. Brown, J. Am. Chem. Soc., 60, 1325 (1938)
II. Kumler, J. Am. Chem. Soc., 60, 855 (1938)
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Fieser and Seligman, J. Am. Chem. Soc., 58, 2482 (1936)
IV. Coles and Dodds, J. Am. Chem. Soc., 60, 853 (1938)
Sommelet, Compt. rend., 157, 852 (1913)
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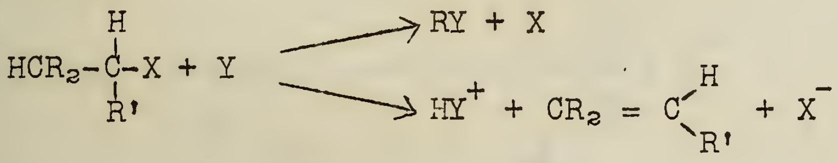
Rupe and Brentano, Helv. Chim. Acta, 19, 581 (1936)

Reported by William S. Emerson
September 28, 1938

THE MECHANISM OF SUBSTITUTION
AT A SATURATED CARBON ATOM

Olson -- University of California
Ingold and Hughes -- University College, London
Hammett -- Columbia University

During the past few years Ingold and Hughes in England and Olson and Hammett in this country have undertaken extensive investigation of the mechanism of reactions involving replacement, as well as elimination, of a group attached to a saturated carbon atom.



(S)

(E)

X may be halogen, SR_2^+, or NR_3^+ while Y may be OH^-, OAc^-, OP^-, halogen$^-$ or NR_3. These reactions are of especial interest since the replacement (S) is the reaction involved in Walden inversion.

It has been found that both reactions (S and E) may take place either first order (S_1 and E_1) or second order (S_2 and E_2) kinetics depending on the nature of the alkyl group, X, Y, and the solvent. Frequently two or more of the reactions proceeded simultaneously but in each case it was possible to analyze the results into their separate components.

The results of the replacement reactions were:

R in CHMeRHal	Homogeneous Reaction Base Catalyzed (S_2)	S_1	Heterogeneous (Ag^+ + AgX(Ag_2O))
C_6H_{13}	Inv.	Inv. and Rac.	Inv. and Rac.
C_6H_5	Inv.	Inv. and Rac.	Inv. and Rac.
COOH, COOR, $CONH_2$	Inv.	(No data)	Inv. and Rac.
CO_2^-	Inv.	Retention	Retention and Rac.

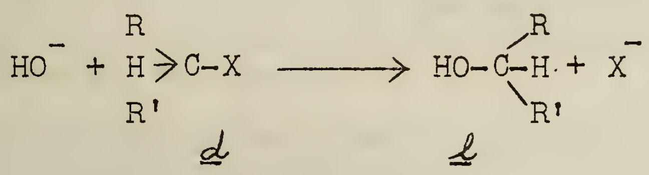
In every case a bimolecular substitution resulted in complete inversion while the unimolecular reaction was usually accompanied by racemization.

The first order elimination reaction (E_1) was characterized by a constant ratio to concurrent first order substitution (S_1) for a series of different halides.

	k_{S_1}	k_{E_1}	Ratio
$(CH_3)_3CCl$	0.71	0.14	5.1
$(CH_3)_3CBr$	32.5	4.69	6.9
$(CH_3)_3CI$	78.5	11.6	6.8

The results are interpreted by the English investigators in the following manner:

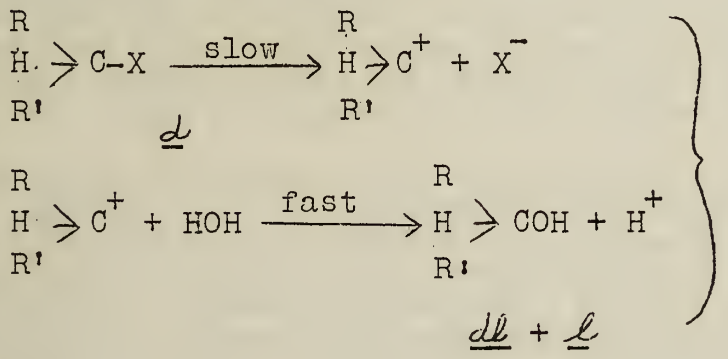
Substitution:

(1) 

$$HO^- + \begin{matrix}R\\H\\R'\end{matrix}\!>C-X \longrightarrow HO-\overset{R}{\underset{R'}{C}}-H + X^-$$

d *l*

(S₂)

(2) 

$$\begin{matrix}R\\H\\R'\end{matrix}\!>C-X \xrightarrow{slow} \begin{matrix}R\\H\\R'\end{matrix}\!>C^+ + X^-$$

d

$$\begin{matrix}R\\H\\R'\end{matrix}\!>C^+ + HOH \xrightarrow{fast} \begin{matrix}R\\H\\R'\end{matrix}\!>COH + H^+$$

dl + *l*

(S₁)

Elimination:

(1) $HO^- + H-CR_2CR_2-X \longrightarrow HOH + CR_2=CR_2 + X^-$ (E_2)

(2) $H-CR_2CR_2-X \xrightarrow{slow} H-CR_2CR_2^+ + X^-$

$H-CR_2CR_2^+ \xrightarrow{fast} H^+ + CR_2=CR_2$ (E_1)

Recently both Hammett and Olson have seriously questioned the first order mechanism involving primary ionization of the C-X bond. They both present excellent evidence that the reactions are really pseudounimolecular since the solvent molecules play an important part in the reaction.

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Hughes, Ingold et al., J. Chem. Soc., 1937, 1177
Farinacci and Hammett, J. Am. Chem. Soc., 59, 2542 (1937)
Olson and Halford, J. Am. Chem. Soc., 59, 2644 (1937)

Reported by C. C. Price
September 28, 1938

DIENE SYNTHESES OF POLYCYCLIC COMPOUNDS

E. Bergmann -- Daniel Sieff Research Institute, Rehovoth,
Palestine
Bachmann and Kloetzel -- University of Michigan

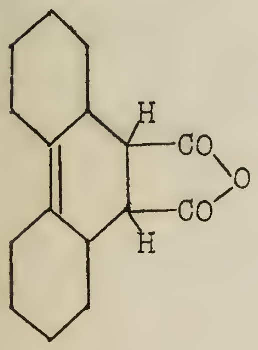
The diene synthesis has been widely applied in recent years for the preparation of polycyclic hydroaromatic and aromatic compounds, and its scope has recently been widened by its application to dienes in which one of the double-bonds is part of an aromatic ring, and to active double-bond reagents of rather complex structure.

The possibilities of employing dicyclohexenyl as a starting material for the synthesis of phenanthrene derivatives have been investigated by Barnett and Lawrence,[1] and Gruber and Adams,[2] and recently their studies have been amplified and extended by Weizmann, Bergmann and Berlin.[3]

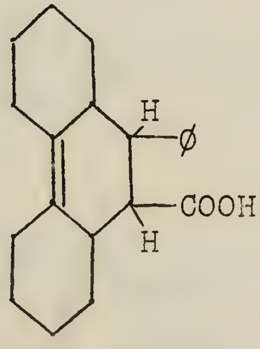
Dicyclohexenyl was found by Gruber and Adams to condense with maleic anhydride and acrolein, while Barnett and Lawrence also prepared the maleic anhydride condensation product as well as products from quinone, α-naphthoquinone and naphthazarin diacetate. Barnett and Lawrence were not able to obtain corresponding products by the use of the corresponding diene prepared from α-tetralone.

Weizmann, Bergmann and Berlin condensed dicyclohexenyl with maleic anhydride (I) and dehydrogenated the product to phenanthrene-9,10-dicarboxylic anhydride, a compound which had been prepared previously by Jeanes and Adams by a different method. Dicyclohexenyl reacted with cinnamic acid to give II, which could be converted to 9-phenylphenanthrene by means of selenium, and to 9-phenylphenanthrene-10-carboxylic acid by the use of sulfur.

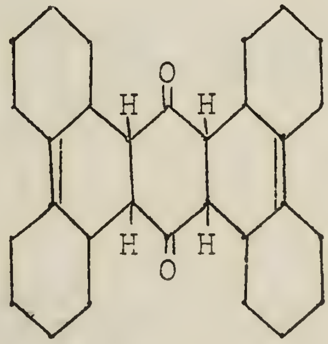
The reaction between quinone and dicyclohexenyl was reinvestigated and it was found that III was formed, along with partially dehydrogenated products formed as a result of the dehydrogenating action of the quinone used. Somewhat similar results were obtained using α-naphthoquinone.



I

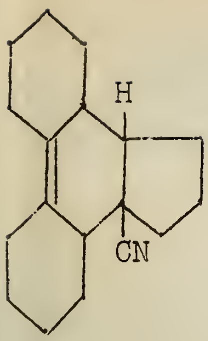


II

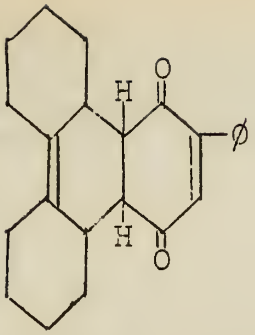


III

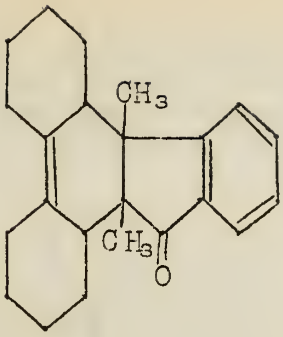
The condensation of 1-cyanocyclopentene-1 with dicyclohexenyl gave a poor yield of IV, while phenylquinone added only one molecule of the diene to give V and 2,3-dimethylindone yielded VI:



IV

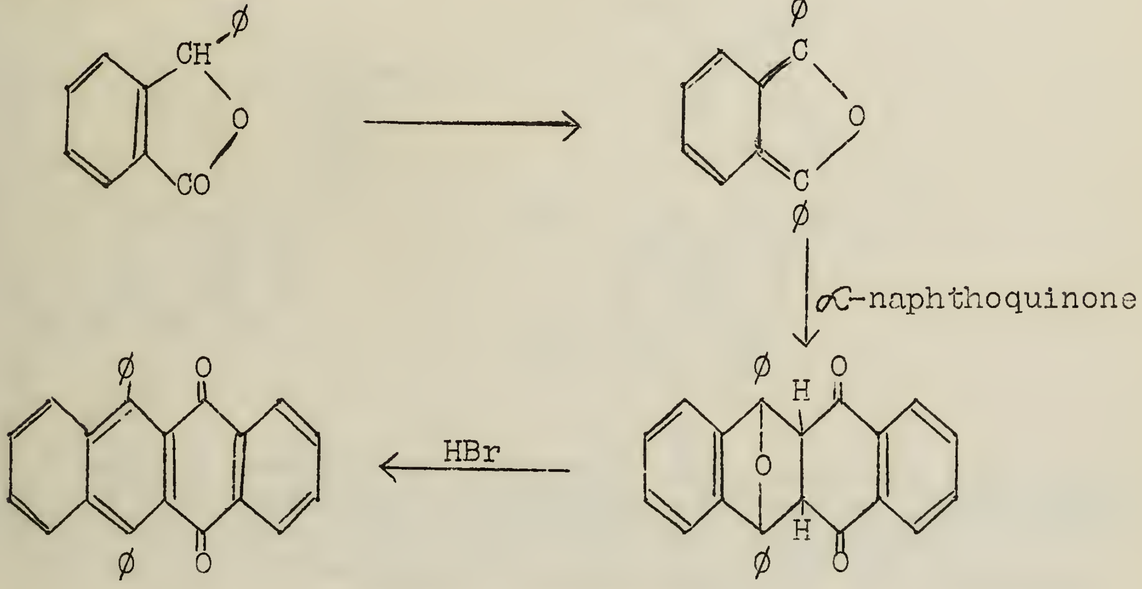


V



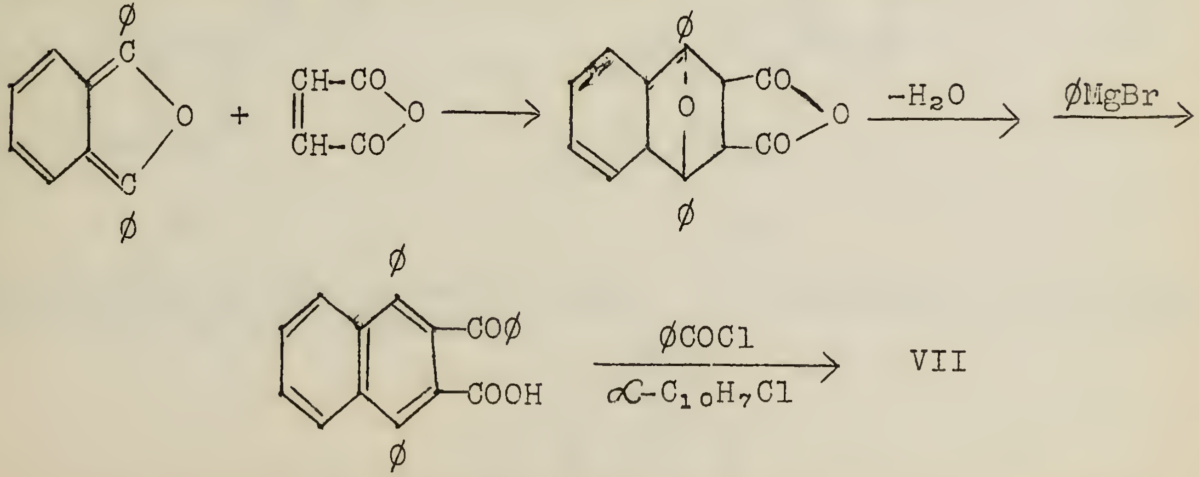
VI

E. Bergmann has described[4] an interesting application of the diene synthesis, leading to the important intermediate (VII) in the synthesis of rubrene:


α-naphthoquinone
HBr

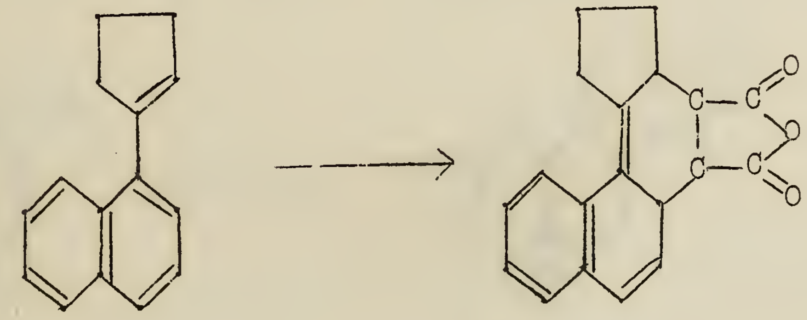
VII

Another route to the same compound is as follows:


$-H_2O$
ØMgBr
ØCOCl
α-$C_{10}H_7Cl$
VII

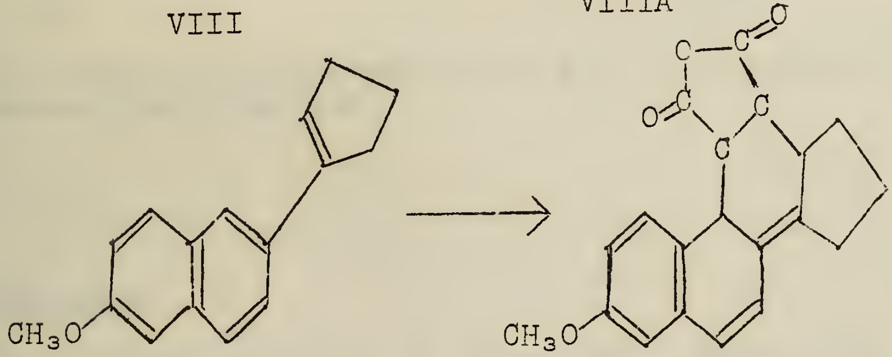
Lately considerable progress has been made in the synthesis of compounds of sterol-like structure.

The success of Cohen and Warren[5] in condensing α-vinylnaphthalene and β-vinylnaphthalene with maleic anhydride led Bergmann and Bergmann[6] to attempt the same reaction using α-cyclopentenyl naphthalene (VIII) and 2-cyclopentenyl-6-methoxy naphthalene (IX).



VIII

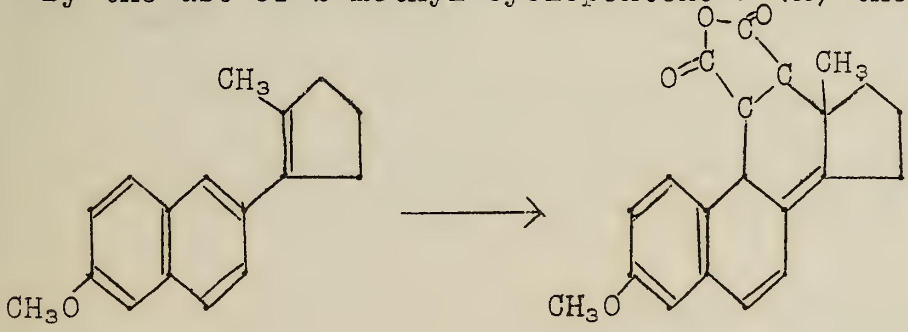
VIIIA



IX

Recently, Bachmann and Kloetzel[7] have repeated these experiments and have succeeded in obtaining addition of maleic anhydride in each case to give VIIIa and IXa respectively.

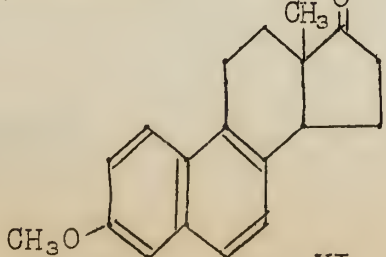
By the use of 2-methyl cyclopentene-1 (X) they produced



X

XA

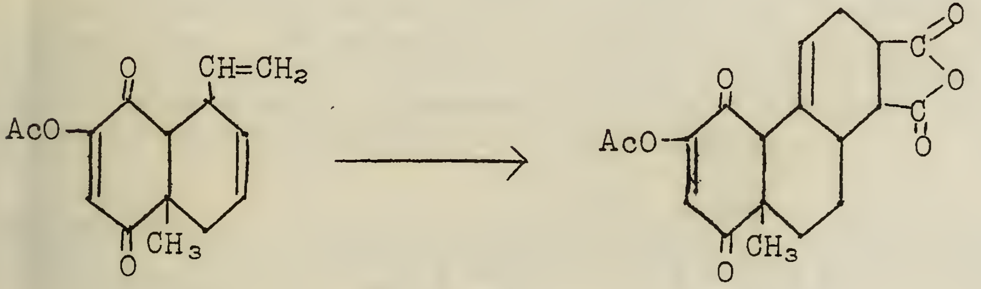
XA containing an angular methyl group. The similarity to equilenin methyl ether (XI) is apparent.



XI

XA could not be dehydrogenated by heating it with sulfur.

Another approach to the sterol problem has been made by Butz.[8] By the addition of hexatriene to 2-methyl-4-acetoxy benzoquinone the product (XII) was capable of undergoing yet another diene



XII

XIII

reaction with maleic anhydride to give a compound (XIII) containing the phenanthrene nucleus.

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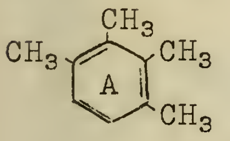
8. Butz, ibid., 216 (1938)

Reported by T. A. Geissman
and C. K. Bradsher
October 5, 1938

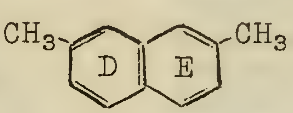
STRUCTURE OF THE TRITERPENES

Ruzicka - die Eidg. Techn. Hochschule Zürich

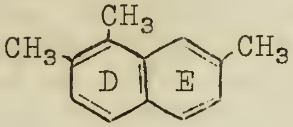
There are found in nature numerous pentacyclic triterpenes, and also hydroxy or dihydroxy derivatives of these pentacyclic triterpenes. The presence of identical skeletons, or ones differing only slightly from each other has been revealed by dehydrogenation experiments. Compounds I-VI give the results of dehydrogenation of various pentacyclic triterpenes.



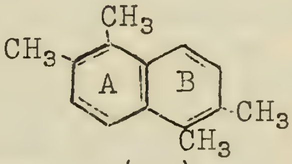
(I)



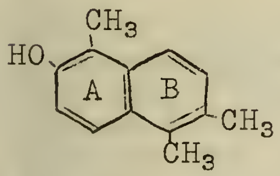
(II)



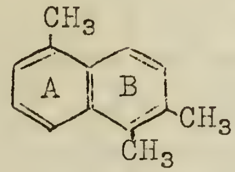
(III)



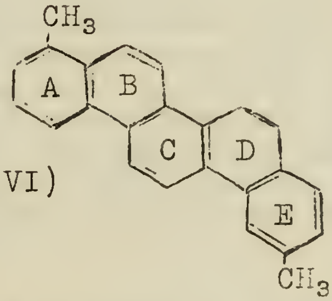
(IV)



(V)

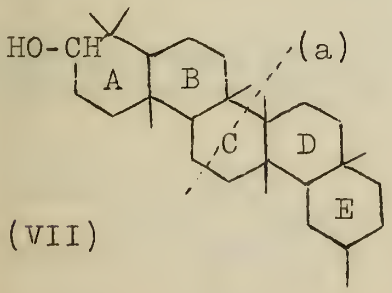


(Va)



(VI)

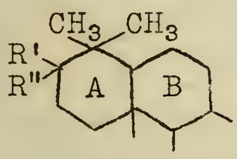
Dehydrogenation products have lost part of the carbon atoms from the original molecule. The naphthalene and benzene derivatives are the result of scission of the molecule in two parts between two of the rings; formation of dimethyl picene (VI) results from the separation of six carbon atoms. Formation of this dimethylpicene (VI) leads to a consideration of a picene nucleus in the pentacyclic triterpenes and the position of the two methyl groups has been definitely established by synthesis. To establish the position of the other six carbon atoms, use is made of the naphthalene and benzene derivatives, and among the various skeletons made possible, only those satisfying the isoprene rule are considered.



(VII)

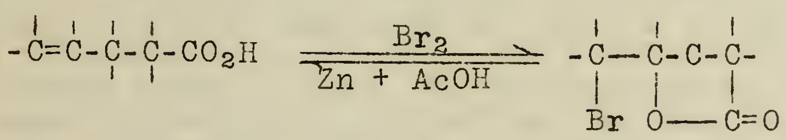
Formula VII, which gives a satisfactory explanation of the characteristic triterpene dehydrogenation products, has been advanced by Ruzicka. Since dehydrogenation results cannot be definite until confirmed by chemical reactions carried out under milder conditions, amyrin and hederagenin are discussed in some detail. In addition to the products of dehydrogenation I-VI, amyrin also yields

2-hydroxy-1,8-dimethylpicene. The picene hydrocarbon (VI) and the above mentioned hydroxydimethylpicene, obtained from amyrin, retain the pentacyclic system and scission at (a) in VII gives an explanation of naphthalene derivatives. Rings D and E account for 2,7-dimethyl- (II) and 1,2,7-trimethylnaphthalene (III), and the naphthol (V) arises from rings A and B. If dehydration of the carbinol occurs before dehydrogenation, migration of one of the "gem" methyl groups becomes feasible and 1,2,5,6-tetramethylnaphthalene (IV) is formed. This assumption regarding the migration of the methyl group is strongly supported by observations on some amyrin derivatives. To prevent dehydration and therefore methyl migration, a hydrocarbon (VIII; R' = R" = H) was prepared by Wolff reduction of the semicarbazone of amyrene (CHOH in VII oxidized to C=O). In accordance with the hypothesis of methyl migration, dehydrogenation of this hydrocarbon did not yield any 1,2,3,4-tetramethylbenzene (I), 1,2,5,6-tetramethylnaphthalene (IV), or phenolic compounds (V), but 1,2,5-trimethylnaphthalene (Va) and 1,8-dimethylpicene (VI) were isolated, along with the usual products from rings D and E. The dehydrogenation products of the compound (VIII; R' = CH_3; R" = OH) were also in agreement with anticipations; 1,2,5,6-tetramethylnaphthalene (IV), in this case definitely from rings A and B, and a new picene homologue, probably 1,2,8-trimethylpicene, were obtained.

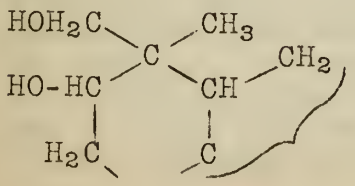


(VIII)

Hederagenin, $C_{30}H_{48}O_4$, is a dihydroxy pentacyclic triterpene acid, and esterification and hydrolysis experiments indicate the tertiary character of the carboxyl group. The acid contains a double bond which resists catalytic reduction but its presence is deduced by the formation of lactones and bromolactones. Bromine has proved a very useful reagent for the detection of double bonds in unsaturated acids and depends on their conversion by bromine into crystalline bromo-lactones, from which the acid is regenerated by Zn + AcOH:

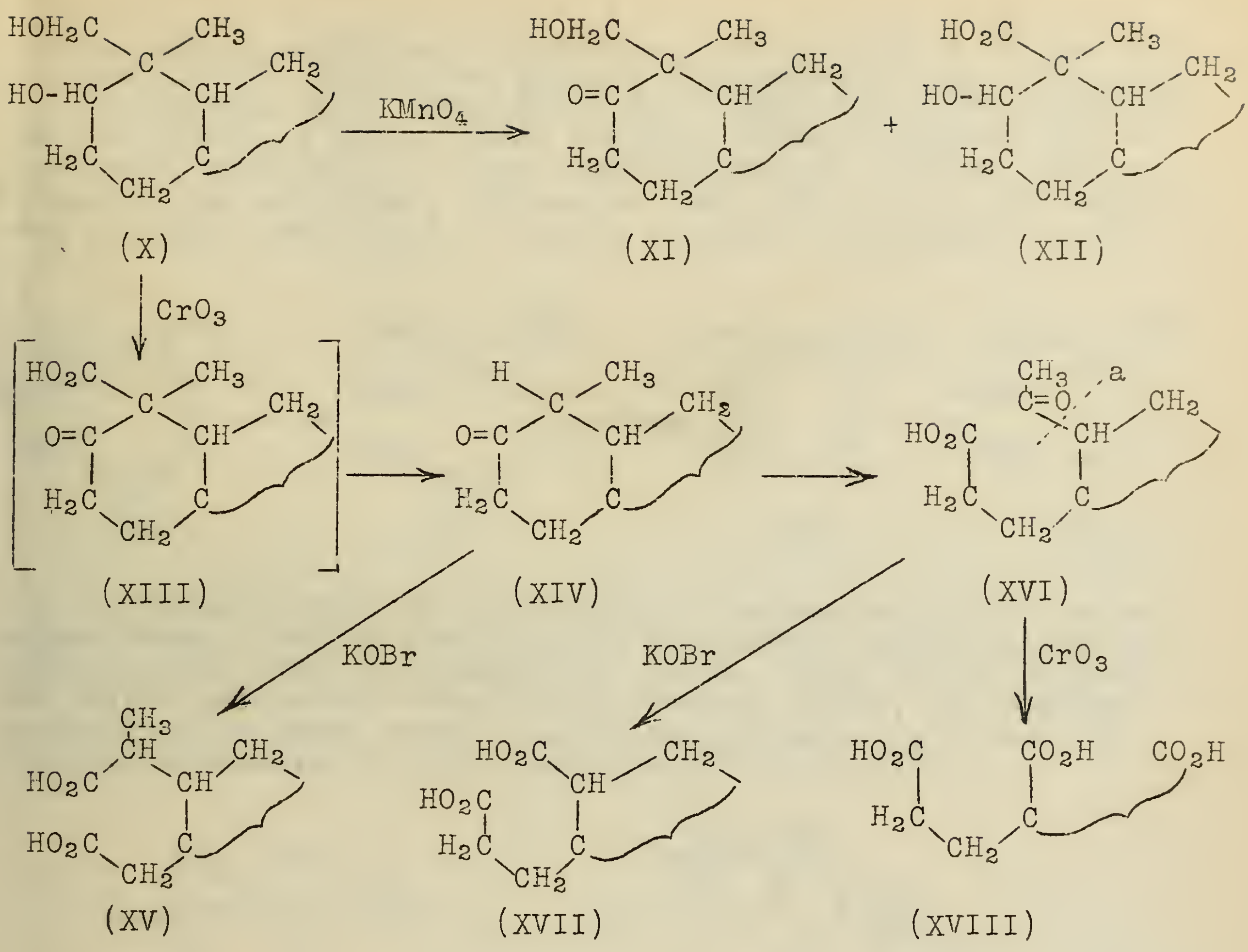


Although rigid proof is lacking, the acids are regarded as γ,δ-unsaturated acids.



(IX)

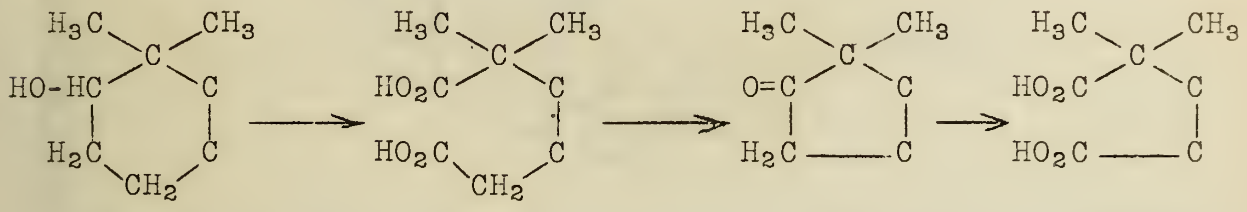
Important evidence concerning the structure of rings A and B has been obtained by oxidizing derivatives in which the carboxyl group is protected by ester or lactone formation. In partial formula IX are found part of rings A and B of the hederagenin molecule deduced by a series of degradations (X-XVIII).



Oxidation of the methyl ester of hederagenin (X) with $KMnO_4$ yields the methyl ester of a hydroxy-keto-acid (XI) and of a dibasic hydroxy-acid (XII), by oxidation of the secondary and of the primary alcohol group respectively. In this compound (X) the secondary hydroxyl group must be near the primary hydroxyl group because CrO_3 oxidation gives the ketone XIV by loss of one carbon atom, presumably as CO_2 from the intermediate β-keto-acid (XIII). Oxidation was carried to completion by Kitasato; the nucleus splits on each side of the C=O in XIV giving two products: a tricarboxylic acid (XV) and a keto-acid (XVI) containing all the carbon atoms. These oxidation products fix the seven carbon atoms indicated in the partial formula IX. Hypobromite oxidizes the keto-acid (XVI) to a tribasic acid XVII. Further oxidation of the ester of XVI with CrO_3, resulting in the elimination of two carbon atoms and the formation of a tetrabasic acid XVIII, is explained by oxidation of XVI at bond a to give a ketone, which yields the tetrabasic acid XVIII by scission between the new ketonic group and the adjoining methylene group of ring B. The properties of this tetrabasic acid indicate that it cannot be a malonic acid derivative (i.e. it is stable with heat); this information will be valuable later in placing the fourth carboxyl group (not shown in formulas IX-XVIII).

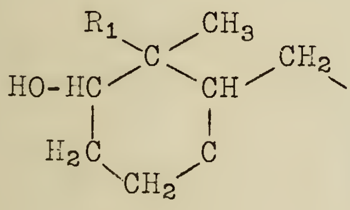
The proof of a methylene group in position 4 of ring A

depends upon experiments on betulin. Part of ring A of betulin is shown in XIX. Oxidation gives a dicarboxylic acid containing 30 carbon atoms (XX). By raising the temperature, $CO_2 + H_2O$ are removed, giving a ketone (XXI) which is itself oxidized to a dicarboxylic acid (XXII). This last compound on heating gave no ketone but an anhydride, indicating that ring A is a six-membered ring and that position 4 of ring A contains a methylene group.

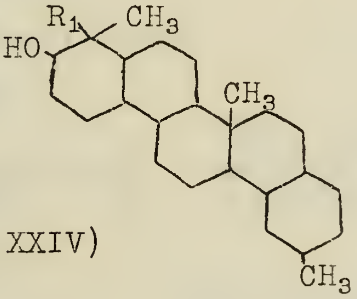


(XIX) (XX) (XXI) (XXII)

In formula XXIII is indicated the arrangement of the nine carbon atoms fixed by reactions of hederagenin and betulin; by including the results of dehydrogenation, 26 of the 30 carbons are fairly definitely established (formula XXIV), the angular methyl group between rings C and D being necessary to account for dehydrogenation to 2,7-dimethylnaphthalene (II).

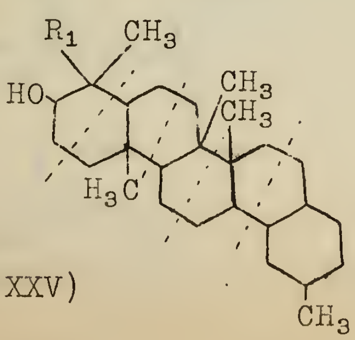


(XXIII)

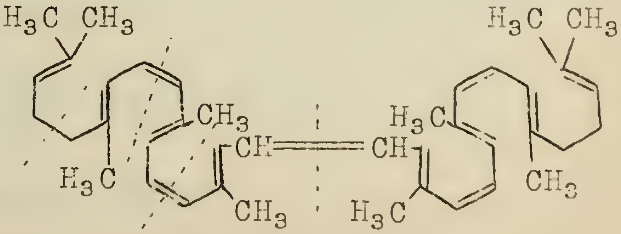


(XXIV)

Somewhere in the rest of the molecule there is known to be a double bond in the γ,δ-position to a tertiary carboxyl group, and four methyl groups in angular positions. Some help on the latter problem may be gained by applying the valuable isoprene rule. If methyl groups are placed between rings A, B, C, and D as shown in XXV, there is formed a regular chain of four isoprene units, as is found in most diterpenes, such as phytol and Vitamin A, and also in the symmetrical polyene terpenes, such as lycopene (XXVI) and β-carotene.

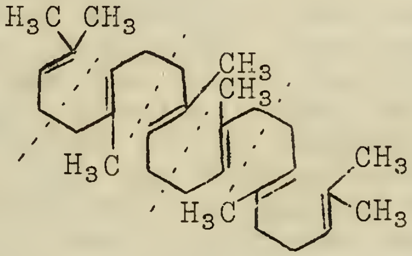


(XXV)



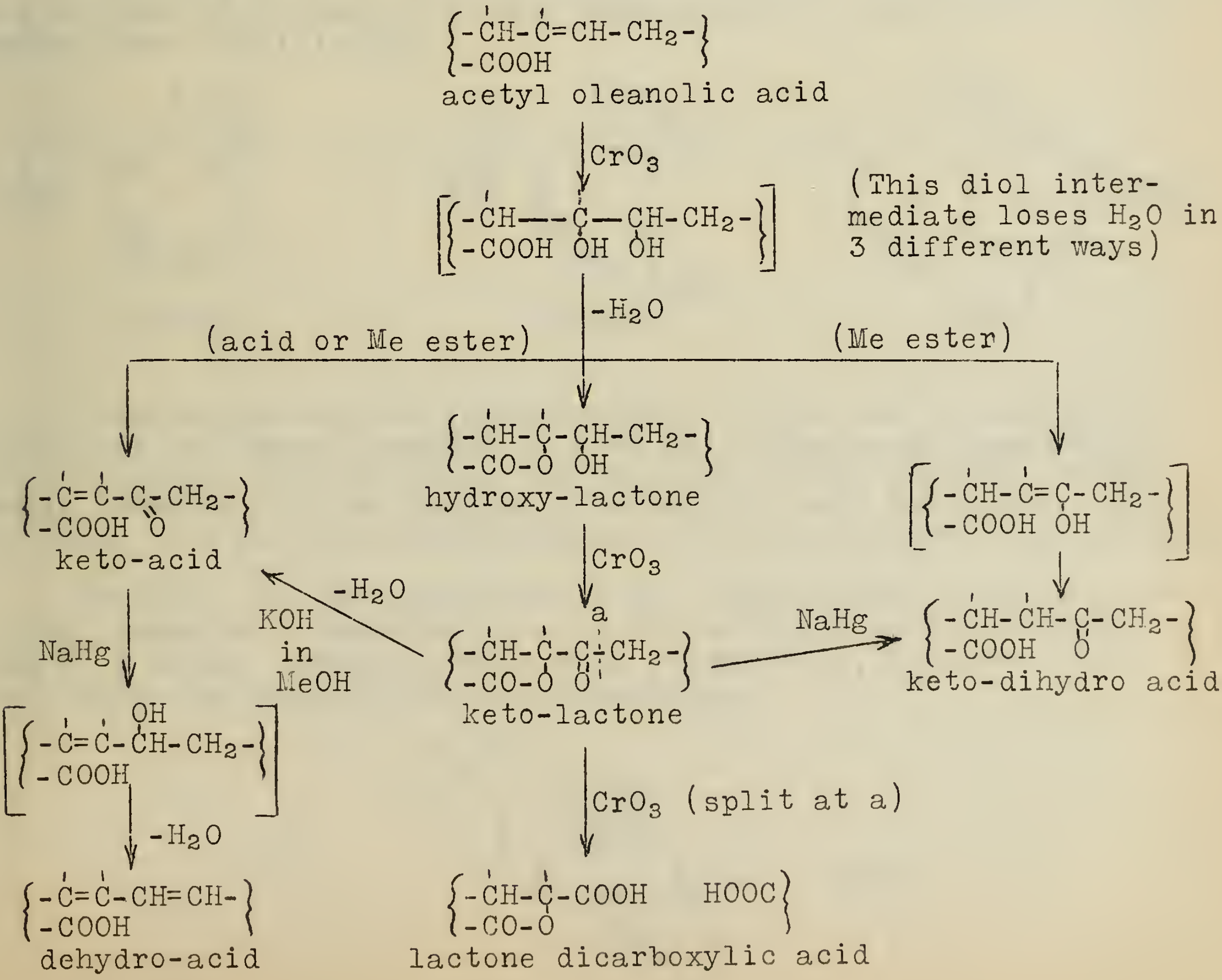
(XXVI)

A similar symmetrical structure containing a straight chain of isoprene units is found in the triterpene hydrocarbon, squalene $C_{30}H_{50}$, whose formula (XXVII) is written so as to show the relationship with rings A, B, and C of formula XXV.


H_3C CH_3
CH_3
CH_3
H_3C
CH_3
H_3C
CH_3

(XXVII)

Kitasato, Ruzicka, and Haworth each have advanced formulas to account for the double bond and the tertiary carboxyl group. Their structures are based on the results of oxidations of oleanolic acid, a monohydroxy pentacyclic triterpene acid. The OH group is protected by acetylation. The exact system -CH-C=CH-CH_2- is found to be necessary by the following series of reactions:


-CH-C=CH-CH_2-
-COOH
acetyl oleanolic acid
CrO_3
-CH—C—CH-CH_2-
-COOH OH OH
(This diol intermediate loses H_2O in 3 different ways)
-H_2O
(acid or Me ester)
(Me ester)
-C=C-C-CH_2-
-COOH O
keto-acid
-CH-C-CH-CH_2-
-CO-O OH
hydroxy-lactone
-CH-C=C-CH_2-
-COOH OH
CrO_3
-H_2O
KOH in MeOH
a
-CH-C-C-CH_2-
-CO-O O
keto-lactone
NaHg
-CH-CH-C-CH_2-
-COOH O
keto-dihydro acid
NaHg
OH
-C=C-CH-CH_2-
-COOH
-H_2O
CrO_3 (split at a)
-C=C-CH=CH-
-COOH
dehydro-acid
-CH-C-COOH HOOC
-CO-O
lactone dicarboxylic acid

Certain properties of these compounds are significant. The keto-acid does not give off CO_2 in boiling tetralin, indicating that it is probably not an alpha or beta-keto acid; it is also reduced by NaHg to a dehydro acid which has two double bonds. The most important derivative is the lactone dicarboxylic acid, whose properties are as follows:

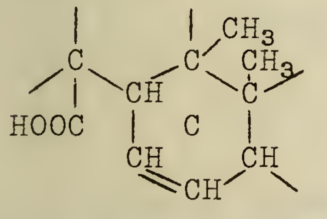
(1) It forms an anhydride; thus the two carboxyls are separated by two, three, or possibly four carbon atoms.

(2) It does not lose CO_2 on heating; this rules out any structure containing a malonic acid derivative.

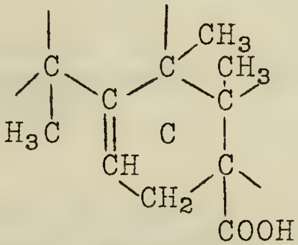
(3) Saponification of its dimethyl ester (m.p. 203°) gives a monomethyl ester (thus one CO_2H is tertiary, the other secondary); when this monomethyl ester is treated with CH_2N_2 and acetylated again, a dimethyl ester of different melting point (273°) is formed; thus saponification has produced an iso-lactone dicarboxylic acid.

(4) The lactone dicarboxylic acid gives 2,7-dimethylnaphthalene (II) on dehydrogenation with selenium; since this naphthalene derivative arises from rings D and E, the double bond cannot be in these rings. It has been previously shown that the double bond cannot be in rings A and B, leaving only ring C in which it can be located.

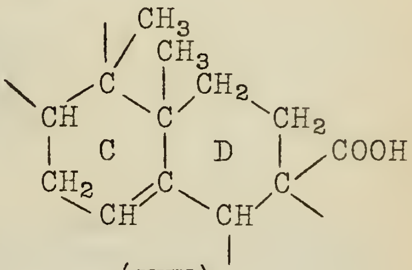
Returning now to a consideration of ring C in formula XXV, it can be seen that there are only three possible positions for the double bond (XXVIII-XXX):



(XXVIII)



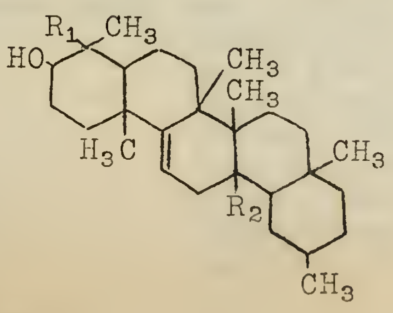
(XXIX)



(XXX)

Kitasato has chosen formula XXVIII, which can be immediately ruled out on several scores: it does not contain any suggestion of the system $-CH-C=CH-CH_2-$; the position of the carboxyl group makes formation of the lactone dicarboxylic acid difficult; and it leads to a malonic acid structure for the tetrabasic acid (XVIII).

Ruzicka, who has done most of the experimental work in this field, supports formula XXIX, with the carboxyl between rings C and D as shown; combining this with formula VII, he gives structure XXXI for the pentacyclic triterpenes:



(XXXI)

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

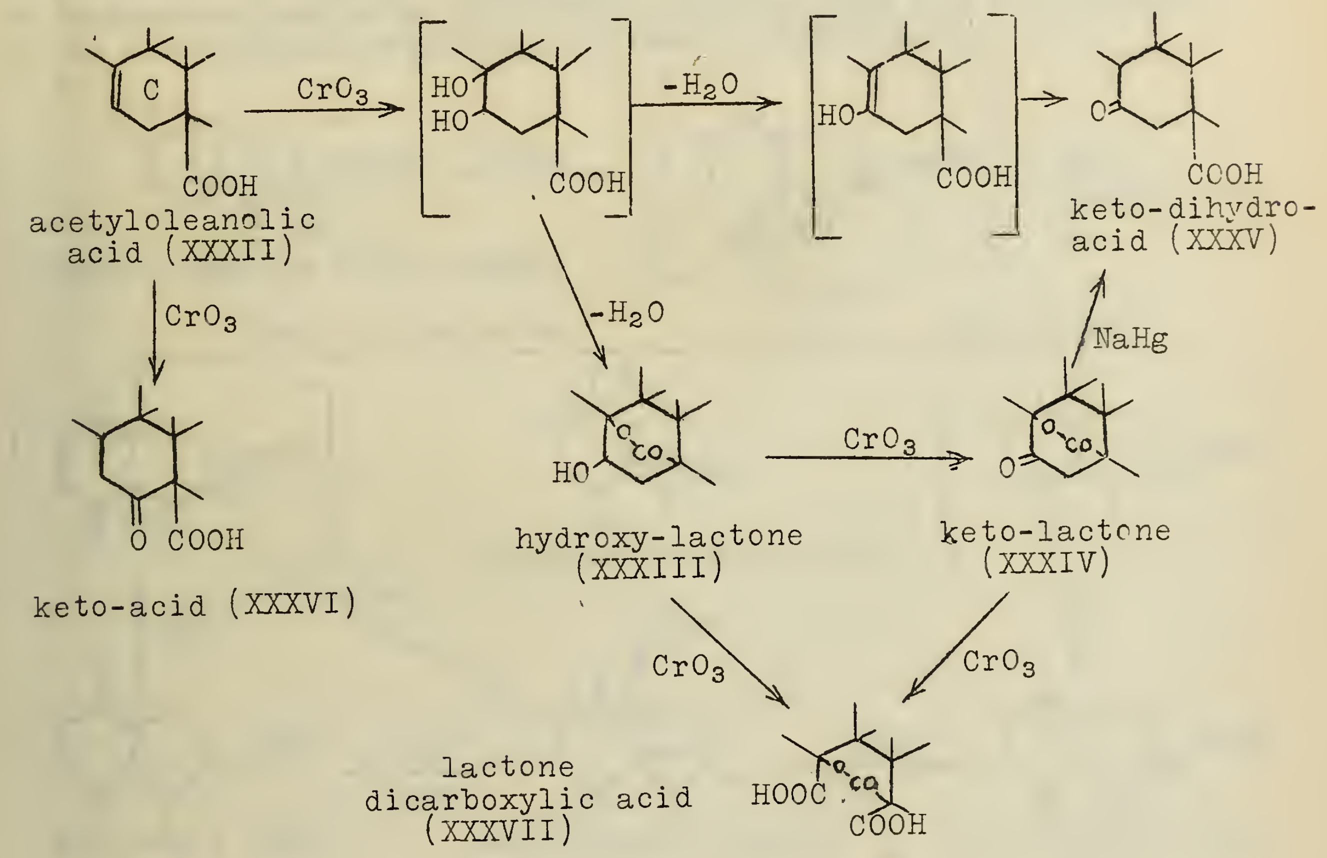
[illegible]

[illegible]

[illegible]

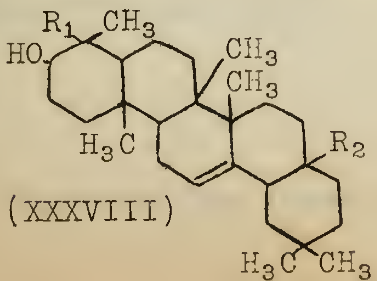
[illegible]

Although this structure of Ruzicka's contains the system $-\dot{C}-\dot{C}=CH-CH_2-$ instead of $-\dot{C}H-\dot{C}=CH-CH_2-$, he is able to formulate the oxidation reactions of acetyloleanolic acid (R_1 = CH_3, R_2 = COOH in XXXI) as shown in partial formulas XXXII-XXXVII:


C
COOH
acetyloleanolic acid (XXXII)
CrO_3
HO
HO
COOH
$-H_2O$
HO
COOH
O
COOH
keto-dihydro-acid (XXXV)
CrO_3
O
COOH
keto-acid (XXXVI)
$-H_2O$
HO
O
CO
hydroxy-lactone (XXXIII)
CrO_3
NaHg
O
O
CO
keto-lactone (XXXIV)
CrO_3
CrO_3
lactone dicarboxylic acid (XXXVII)
HOOC
O
CO
COOH

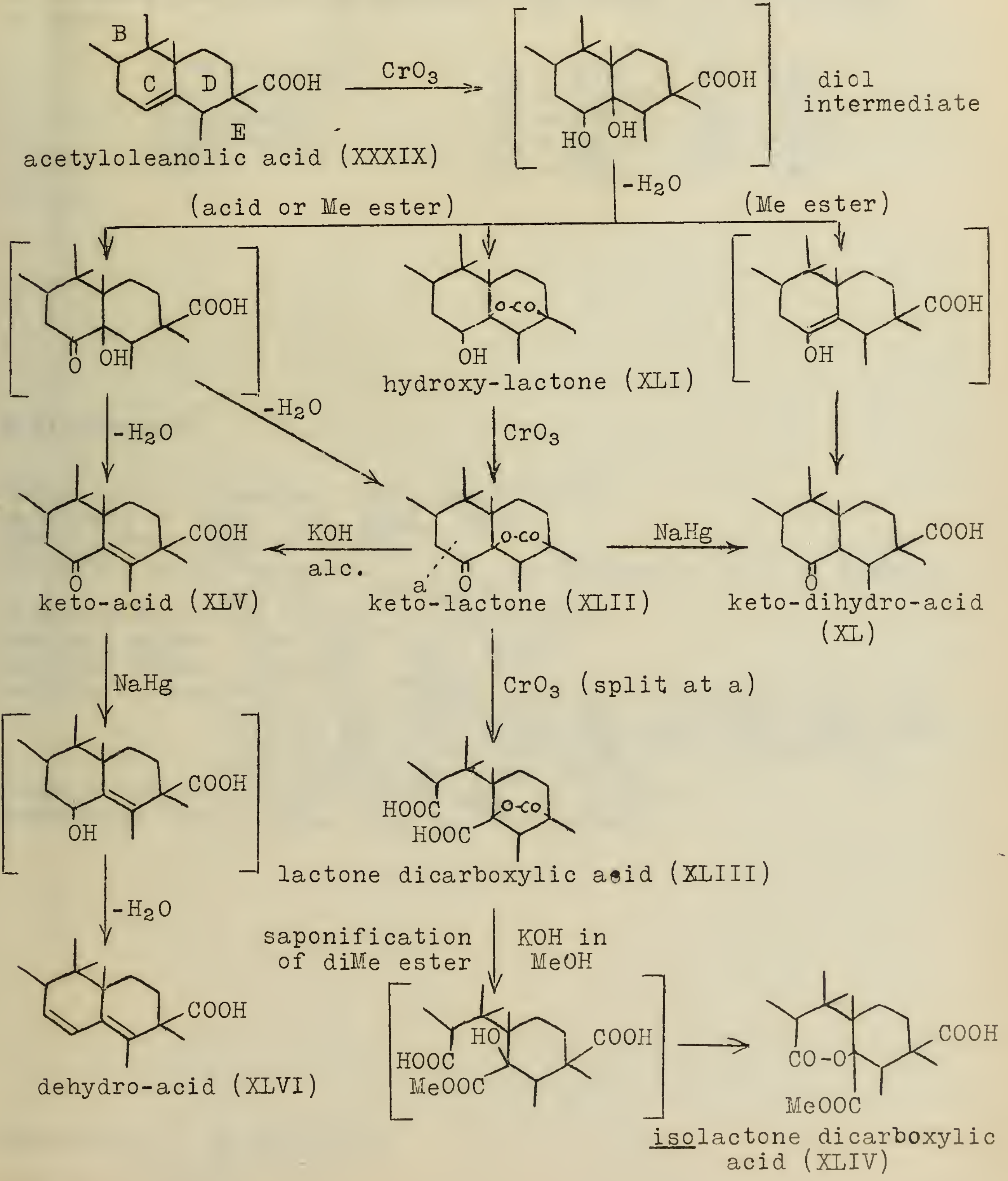
Several objections can be raised to this formulation of Ruzicka's, rendering it unacceptable: (1) XXXI does not contain the system $-\dot{C}H-\dot{C}=CH-CH_2-$; (2) formation of the keto-acid (XXXVI) from the keto-lactone (XXXIV) with alcoholic KOH involves a shift of the keto group, which is very difficult to explain; (3) the keto-acid (XXXVI) is a β-keto-acid and should lose CO_2 with boiling tetralin; (4) no formula for the dehydro-acid (obtained from the keto-acid XXXVI by reduction) is possible; (5) the lactone dicarboxylic acid (XXXVII) is a malonic acid derivative, and should lose CO_2; (6) no isolactone dicarboxylic acid structure can be given; (7) all three carboxyl groups in the lactone dicarboxylic acid (XXXVII) are tertiary (see top P. 6, this abstract).

After reviewing the experimental facts, Haworth postulated a pentacyclic triterpene structure (XXXVIII) containing the formula XXX. This formula XXXVIII would yield the same dehydrogenation products from rings A and B as formula XXXI. The principle dehydrogenation products obtained from rings D and E are 2,7-dimethylnaphthalene (II) and 1,2,7-trimethylnaphthalene (III). The former (II)


R_1
CH_3
HO
CH_3
CH_3
H_3C
R_2
H_3C
CH_3

(XXXVIII)

is obtained from XXXVIII by loss of one of the "gem" methyl groups in ring E, and the trimethylnaphthalene (III) is obtained by migration of this methyl, a phenomenon already found in amyrin. All the oxidation reactions of acetyloleanolic acid can be accounted for on a reasonable basis as outlined in XXXIX-XLVI.


B
C
D
E
COOH
acetyloleanolic acid (XXXIX)
CrO_3
COOH
HO
OH
diol intermediate
$-H_2O$
(acid or Me ester)
(Me ester)
COOH
O
OH
o-co
OH
hydroxy-lactone (XLI)
COOH
OH
$-H_2O$
$-H_2O$
CrO_3
COOH
O
keto-acid (XLV)
KOH
alc.
o-co
a
O
keto-lactone (XLII)
NaHg
COOH
O
keto-dihydro-acid (XL)
NaHg
CrO_3 (split at a)
COOH
OH
HOOC
HOOC
o-co
lactone dicarboxylic acid (XLIII)
$-H_2O$
saponification of diMe ester
KOH in MeOH
COOH
dehydro-acid (XLVI)
HO
COOH
HOOC
MeOOC
COOH
CO-O
MeOOC
isolactone dicarboxylic acid (XLIV)

Whatever the formula accepted for the pentacyclic triterpenes,

the correlation between several members of the series is definitely fixed on the basis of reactions relating them to each other. In this way, either formula XXXI (Ruzicka) or XXXVIII (Haworth) could be adopted for these triterpenes, indicating the appropriate changes:

Oleanolic acid	$R_1 = CH_3$	$R_2 = COOH$
Hederagenin	$R_1 = CH_2OH$	$R_2 = COOH$
Gypsogenin	$R_1 = CHO$	$R_2 = COOH$
Erythrodiol	$R_1 = CH_3$	$R_2 = CH_2OH$
Amyrin	$R_1 = CH_3$	$R_2 = CH_3$

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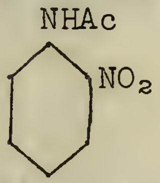
Reported by L. N. Whitehill
E. H. Riddle
October 12, 1938

THE ASSOCIATING EFFECT OF THE HYDROGEN ATOM

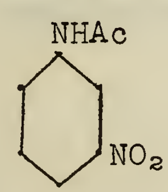
Chaplin and Hunter -- University College, Leicester

The molecular weight measurements of v. Auwers and his co-workers, and of Meldrum and Turner provide ample evidence that amides, anilides, and sulfonamides are associated in solution. Chaplin and Hunter extended this study to a series of N-substituted amides, anilides, and sulfonamides, and derivatives, and their results clearly show that molecular association is general in those compounds containing a free amide-hydrogen atom, but that replacement of both amide-hydrogen atoms effectively checks association. This dependence upon the presence of the amide-hydrogen atom clearly points to hydrogen-bond formation as the cause of association in amides.

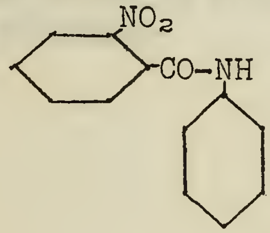
Many anilides possessing an *ortho*-substituent, however, are not associated, and this behavior is evidently due to intramolecular interference with the tendency of the -CO•NH- group to accept and to donate hydrogen; it is significant that in the majority the *o*-substituents so effective are hydrogen acceptors so constituted that six-membered chelation involving hydrogen is easily achieved. For example, while *o*-nitroacetanilide (I) is not associated, its *m*-isomer (II) is strongly so; while *o*-nitrobenzanilide (III) is associated, benzo-*o*-nitroanilide (IV) is not.



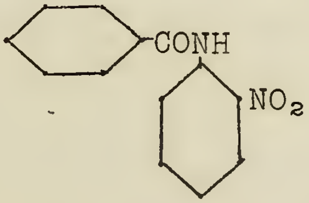
I



II

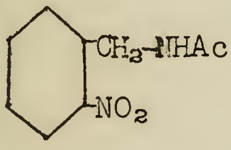


III

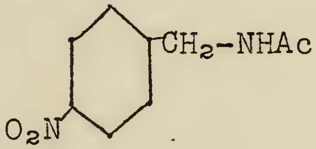


IV

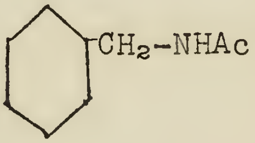
In contrast, acet-*o*-nitrobenzylamide (V), where chelation would not be expected, is as strongly associated as its *p*-isomer (VI), and as acetobenzylamide (VII).



V

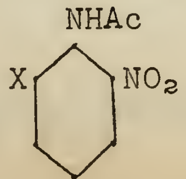


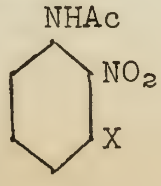
VI



VII

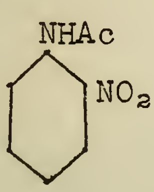
Substitution in the second *ortho*-position of *o*-nitroacetanilide (VIII), prevents chelation; this is interpreted by Chaplin and Hunter as evidence of restricted rotation about the N-nuclear single bond in 2,6-disubstituted acetanilides.



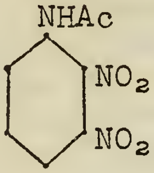


Substitution in the 3-position of o-nitroacetanilide (IX) also markedly decreases its chelating; this is interpreted by Chaplin and Hunter as evidence of a restricting effect of the 3-substituent on the adjacent nitro group, rotating it to a position noncoplanar with the benzene nucleus, thus preventing chelation.

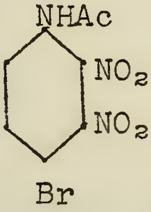
Chaplin and Hunter also claim to have evidence for the transmission of steric effects along the four adjacent groups in such compounds as 2,3-dinitro-4-X-acetanilide; for example, 2,3-dinitroacetanilide (XI) is not chelated, while 2-nitroacetanilide (X) is chelated; however, 2,3-dinitro-4-bromoacetanilide (XII) is again chelated.



X



XI



XII

In Chaplin and Hunter's studies, chelation and association are deduced from wet melting point depression and from cryoscopic behavior in naphthalene solution.

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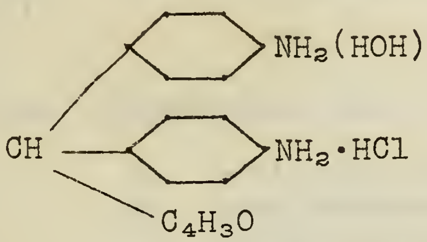
(Mascarelli and Benati, Gazzetta, 39B, 642 (1909))
Chaplin and Hunter, J. Chem. Soc., 1937, 1114; 1938, 375, 1034.

Reported by L. Dankert
October 19, 1938

SPLITTING OF FURANS WITH AROMATIC AMINES

Borsche, Leditschke, and Lange -- Universität
Frankfort a. M.

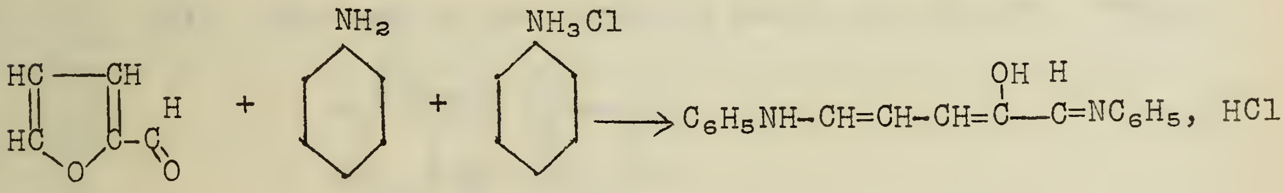
In 1870 Stenhouse observed that a red color was produced when furfural was treated with aniline and HCl. He isolated a compound with the formula $C_{17}H_{18}O_2N_2$. Similar reactions were obtained with furfural and toluidine and with furfural and naphthylamine. In 1887 H. Schiff advanced the theory that a furyldiphenyl-methane was formed in this reaction.



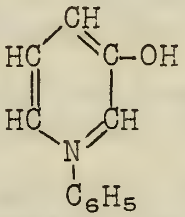
Zincke and Mühlhausen, in 1905, observed a similarity between this compound and the substituted pentadiene which they had made from dinitrophenyl pyridinium chloride.

ArNH-CH=CH-CH=CH-CH=NAr, HCl

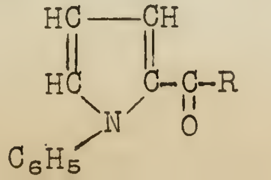
They found that the reaction which occurred was as follows:



This compound was very hard to isolate and purify since it easily splits out aniline and forms 1-phenyl-3-hydroxy pyridinium chloride.



Borsch and coworkers tried this reaction on several 2-furylaryl ketones which they had prepared. The reaction mixtures turned red, but in order to get sufficient yields it was necessary to carry out the reaction in a bomb tube. Under these conditions no pentadiene was formed, but good yields (40 to 60 per cent) of the substituted pyridinium chlorides were obtained. By careful separation they also isolated some pyrrole derivatives in some cases.



Borsche and coworkers investigated the following compounds:

1. 2-benzoyl furan
2. 2-(4-methyl benzoyl)furan
3. 2-(4-methoxy benzoyl)furan
4. 2-(3,4-dimethoxybenzoyl) furan
5. 2-(4-hydroxybenzoyl)furan
6. 2-(2,4-dihydroxybenzoyl) furan
7. furil
8. 2-acetyl furan
9. 2-propionyl furan
10. 2-phenacetyl furan
11. 2-hydrocinnamoyl furan
12. 2-cinnamoyl furan

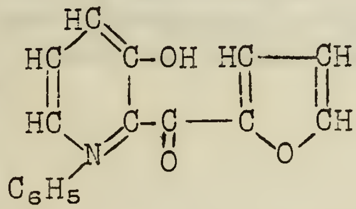
The amines other than aniline investigated were:

1. 4-methoxyaniline
2. 4-bromoaniline
3. 4-nitroaniline
4. 4-aminophenol
5. 3-nitroaniline
6. 3-aminophenol
7. 2-methylaniline
8. methyl anthranilate

Their results were as follows:

(A) With ketones 1-4 and 8-11, 2-aryl-1-phenyl-3-hydroxy pyridinium chlorides were obtained. With ketones 14 a small quantity of 1-phenyl-2-acyl pyrrols were obtained.

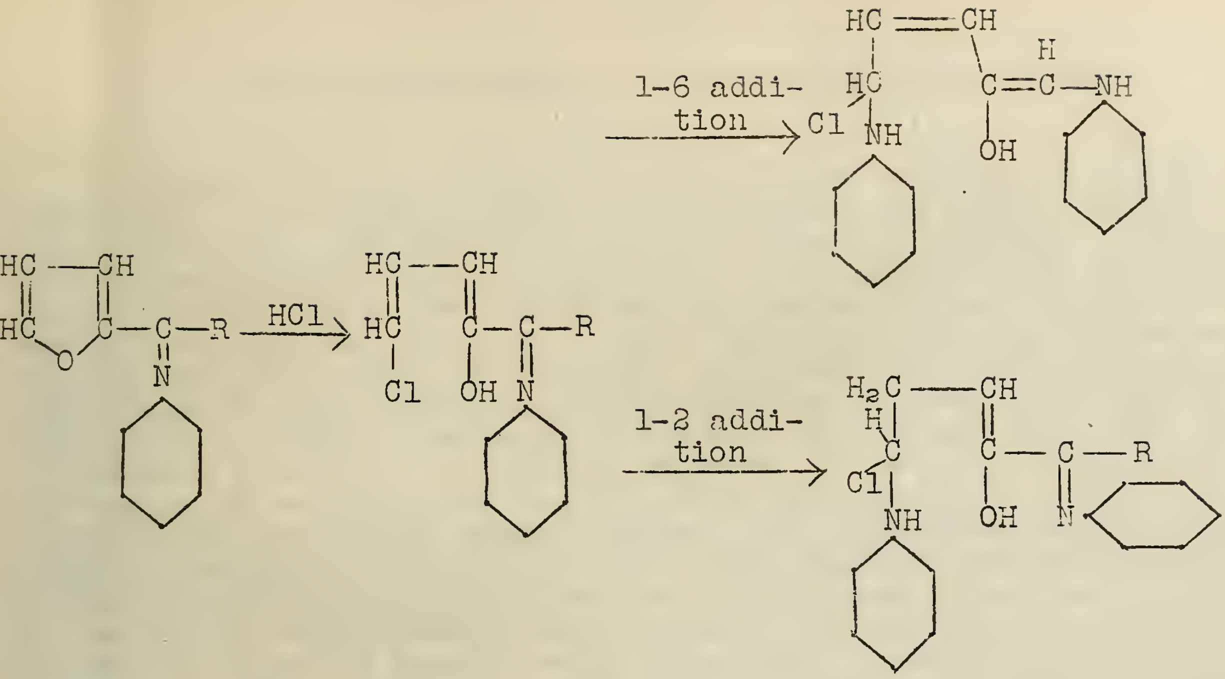
(B) Only one of the rings in furil was opened, forming



(C) With ketones 5, 6, and 12 were obtained, as far as any reaction occurred, only resinous pyridinium chlorides.

(D) Anthranilic ester and 3-aminophenol were the only amines investigated that did not split the furan ring.

By applying the bomb method to the simplest case, furfural and aniline, the yield of the pyridinium chloride was doubled. (Increased to 40 per cent). Since a mole of aniline is split out in the second step of the reaction, Borsche hoped to decrease polymerization and increase the yield by using less than a mole of aniline. This did not increase the yield, however. This indicates that the furan ring is opened up in the furfural-aniline compound and not in furfural itself. Borsche believes that the HCl opens up the ring and that a mole of aniline adds onto the conjugated system. It can add on in a 1-2 or a 1-6 manner.



The 1-6 addition product splits out aniline and forms a substituted pyridinium chloride. The 1-2 addition product forms a pyrrole derivative by splitting out water and by hydrolysis.

The ketones 1-4 were prepared from pyromucic acid chloride by the Friedel-Craft synthesis. Ketone 5 was made by Gilman's method by the transformation of phenyl pyromucic ester with $AlCl_3$. Ketone 6 was prepared by Bauer from pyromucic nitrile by reaction with resorcinol.

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Ann., 239, 349 (1887)

Reported by C. R. Lee
October 19, 1938

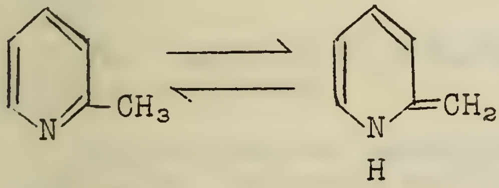
TAUTOMERISM OF PYRIDINE HOMOLOGS

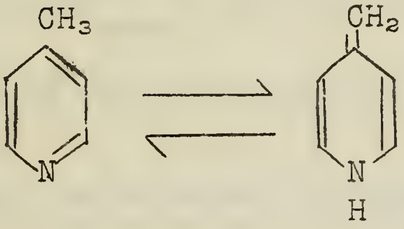
PYRIDINE SERIES SYNTHESES

A. E. Tschitschibabin -- Pasteur Institute, Paris

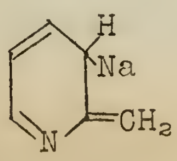
In 1922 Mills and Smith pointed out the similarity between the reactions of the methyl group of α-picoline and other similar heterocyclic systems, and the methyl group of methyl ketones. There are two isomeric α-picolines, depending on the position of the double bond. If the bonds are fixed, as in 1-methylisoquinoline and 3-methylisoquinoline, then the former should contain an active methyl group, but the latter should not. This was verified experimentally. The study of these structures was taken up by Bergstrom in 1931. The system >C=N- is related to ammonia in the same way that >CH=O is related to water. A typical property of ketones with αH is the formation of salts of the enol form by the agency of alkali metals, alcoholates, or alkali metal amides. The analogous reaction is possible with dimethylquinoxaline. The product reacts with EtI to produce 2,3-di-*n*-propylquinoxaline. The preparation was extended to quinoline and pyridine derivatives. For example, the amides of K, Na, Li, reacted readily with solutions of quinaldine in liquid ammonia to give solutions of the salt. These salts were unstable to heat, and always retained ammonia when isolation was attempted. Reaction of the salt with alkyl halides produced lengthened side chains.

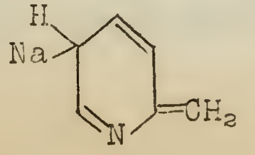
The tautomerization of pyridine was studied in 1927 by Tschitschibabin, and again in 1936-1938. The tautomerization of the picolines is proposed:

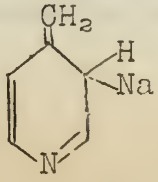




The formation of alkali metal salts is then possible. The experimental method for preparation of pyridine homologs involves mixing sodamide and the pyridine base. The salt formation is reversible, and limited by an equilibrium which varies with the base. Then the slow addition of an alkyl halide disturbs the equilibrium and allows the reaction to proceed. Two reactions interfere: formation of quaternary salts and loss of halogen acid to form unsaturates. Of the halides, chlorides give best results. With regard to ease of salt formation, γ-picoline is better than α-picoline. One side reaction occurring occasionally is the formation of disubstituted derivatives. Also, in some cases small amounts of unknown isomeric bases were isolated, probably from a different type of tautomerization:



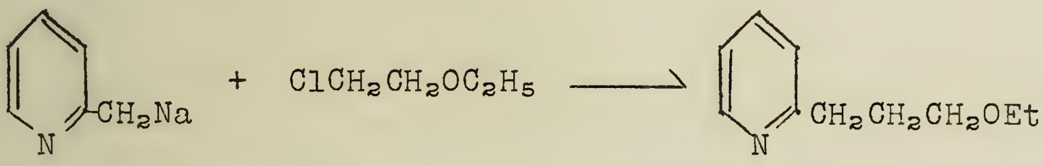




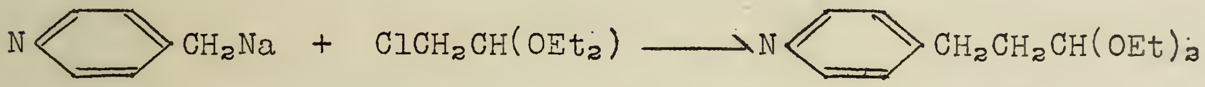
The yields are usually not less than 40 per cent and are mostly 50-60 per cent. Many new compounds are described, the bases used being chiefly α- and γ-picoline, although α,α'-dimethyl pyridine, γ-ethylpyridine, β-collidine, lepidine, and quinaldine were occasionally used. The halides included benzyl chloride, β-phenylethyl chloride, n-butyl chloride, isobutyl chloride, cyclohexyl bromide, allyl bromide, ethyl chloride, ethyl bromide, and isopropyl chloride.

The study was extended to higher molecular weight products, and with cetyl chloride a long side chain ($C_{16}H_{33}$) was added to α- and γ-picoline. Cyclohexyl and cyclopentyl side chains were also added.

The same method was applied to other halides with success. β-Chloroethyl ether and α-picoline, γ-picoline, and β-collidine gave the expected products:



For the acetal of chloracetaldehyde and γ-picoline:



The compound $Et_2NCH_2CH_2Cl$ gave good results with α-picoline and with lepidine.

Polyhalides as methylene chloride and ethylene chloride gave no results. Tetrachloroethylene gave a product which polymerized very readily.

These metal derivatives should give reactions typical of organometallic compounds. Thus, Zeigler and Zeiser allowed the lithium derivative of quinaldine to react with benzophenone to give practically a quantitative yield of the tertiary alcohol 1,1-diphenyl-2-(quinolyl-2-)-ethanol. The experimental procedure of Tschitschibabin works very well in cases where the free sodamide does not complicate the reaction. Benzophenone gave the expected products with quinaldine and α-picoline, but aliphatic ketones condensed with themselves. Benzaldehyde and α-picoline gave a Cannizzaro reaction. Benzoic esters gave benzoic acid and benzamide, with some phenyl-α-picolyl ketone. Benzonitrile and α-picoline gave mostly cyaphenine, but in the case of γ-picoline a lower temperature was possible and a good yield of γ-phenacylpyridine was obtained.

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Bull. soc. chim., (5), 5, 429, 436 (1938); (5), 3, 1607 (1938)
Rec. trav. chim., 57, 582 (1938)

Reported by E. C. Horning
October 26, 1938

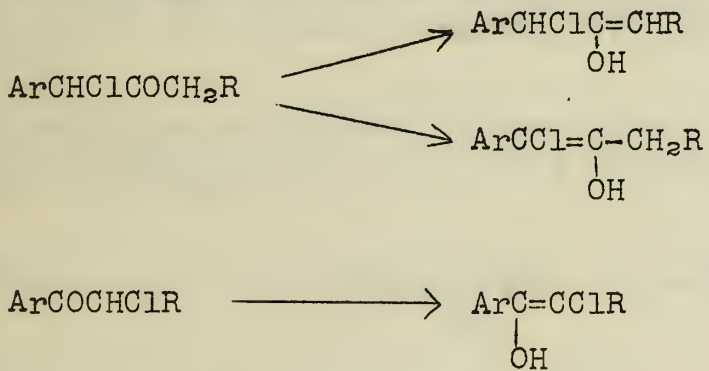
REACTIVITIES OF SUBSTITUTED α-CHLORO KETONES AND THE MECHANISM OF CERTAIN REACTIONS

Richards -- University of Nancy

α-Chloro ketones of the type $ArCHClCOCH_2R$ possess a much more reactive halogen than ketones of the type ArCOCHClR. Richards attributes this difference in reactivity to the fact that the former through enolization by means of a hydrogen atom on the α-carbon containing no halogen give rise to halides of the allyl type while the latter form only enols of the vinyl halide type.

Richards suggests that certain abnormal reactions of the ketones $ArCHClCOCH_2R$ are due to the intermediate formation of an enol of the allyl type.

The fact that chloroacetone reacts readily with sodium acetate in acetic acid solution and with benzene in the presence of aluminum chloride to form $CH_3CO_2CHCOCH_3$ and $CH_3COCH_2C_6H_5$, respectively, while ω-chloroacetophenone is without action on both reagents led Richards to study and contrast ketones of the type $ArCHClCOCH_2R$ with those of the type ArCOCHClR. He found that like chloroacetone, the ketones $ArCHClCOCH_2R$ reacted readily with sodium acetate and with benzene in the presence of $AlCl_3$ while those of the type ArCOCHClR either did not react at all or gave yields of less than 10 per cent. He attributes this difference in reactivity to the enol forms.

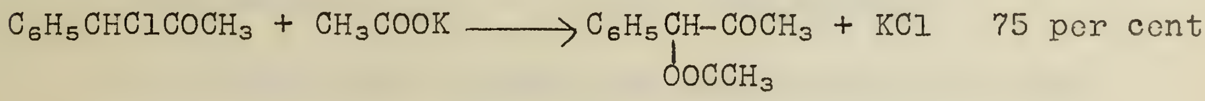


$$ArCHClCOCH_2R \rightarrow ArCHCl\underset{OH}{C}=CHR$$

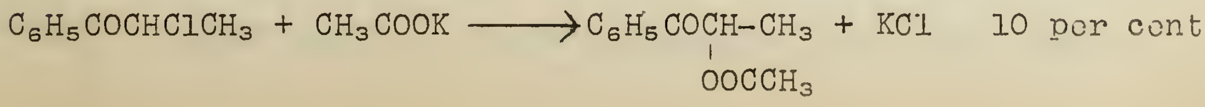
$$ArCHClCOCH_2R \rightarrow ArCCl=\underset{OH}{C}-CH_2R$$

$$ArCOCHClR \longrightarrow Ar\underset{OH}{C}=CClR$$

Thus the ketone $ArCHClCOCH_2R$ contains a potential allylic halogen while the ketone ArCOCHClR can form only a halide of the vinyl type on enolization. Thus, 1-phenyl-1-chloropropanone reacts with anhydrous potassium acetate to the extent of 75 per cent while α-chloropropiophenol reacts to the extent of 10 per cent under identical conditions.



$$C_6H_5CHClCOCH_3 + CH_3COOK \longrightarrow C_6H_5\underset{OOCCH_3}{CH}-COCH_3 + KCl \quad \text{75 per cent}$$



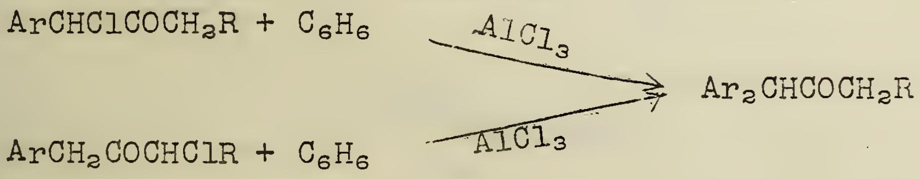
$$C_6H_5COCHClCH_3 + CH_3COOK \longrightarrow C_6H_5CO\underset{OOCCH_3}{CH}-CH_3 + KCl \quad \text{10 per cent}$$

The number of aryl radicals attached to the halogenated α-carbon atom also affects the mobility of the halogen atom. α-Chlorophenylbenzyl ketone, $C_6H_5CHClCOC_6H_5$, was found to be intermediate in reactivity, forming the corresponding acetate to the extent of 33 per cent, indicating that it was not the phenyl group alone that was responsible for the reactivity of the ketones $ArCHClCOCH_2R$.

If the enol form is really an intermediate then the two ketones, $ArCHClCOCH_2R$ and $ArCH_2COCHClR$, due to the ionization of the intermediate enol forming the tripolar ion

$$\mathrm{Ar\overset{+}{C}H\overset{-}{C}(OH)\overset{+}{C}HR}$$

should give the same product with benzene in the presence of aluminum chloride. Richards found this to be true.

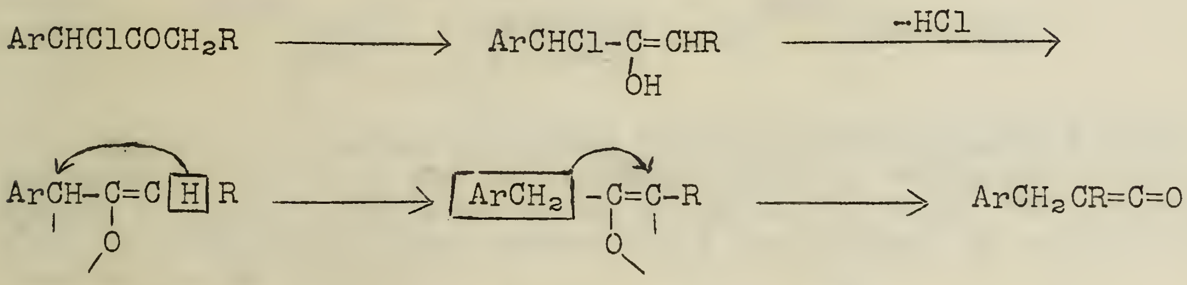


$$\mathrm{ArCHClCOCH_2R + C_6H_6 \xrightarrow{AlCl_3} Ar_2CHCOCH_2R}$$
$$\mathrm{ArCH_2COCHClR + C_6H_6 \xrightarrow{AlCl_3} Ar_2CHCOCH_2R}$$

The tripolar ion is stabilized by resonance of the double bond.

The ketones $ArCOCHClR$ were without action on benzene in the presence of aluminum chloride or gave very poor yields (less than 10 per cent).

With anhydrous potassium hydroxide the ketones $ArCHClCOCH_2R$ yielded the potassium salt of the acid $ArCH_2CHRCOOH$. The following is Richards' mechanism.



$$\mathrm{ArCHClCOCH_2R \longrightarrow ArCHCl{-}\underset{OH}{C}{=}CHR \xrightarrow{-HCl}}$$
$$\mathrm{ArCH{-}\underset{O}{C}{=}C\boxed{H}R \longrightarrow \boxed{ArCH_2}{-}\underset{O}{C}{=}C{-}R \longrightarrow ArCH_2CR{=}C{=}O}$$

Hydration of the resulting ketene produces the acid.

$$\mathrm{ArCH_2CR{=}C{=}O + H_2O \longrightarrow ArCH_2CHRCOOH}$$

If the enol, $\mathrm{ArCCl{=}\underset{OH}{C}{-}CH_2R}$ had been evolved, the acid $RCH_2CH(Ar)COOH$ should have been formed by a similar scheme.

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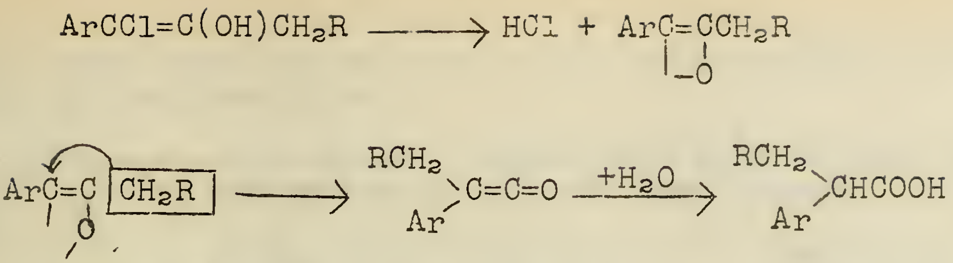
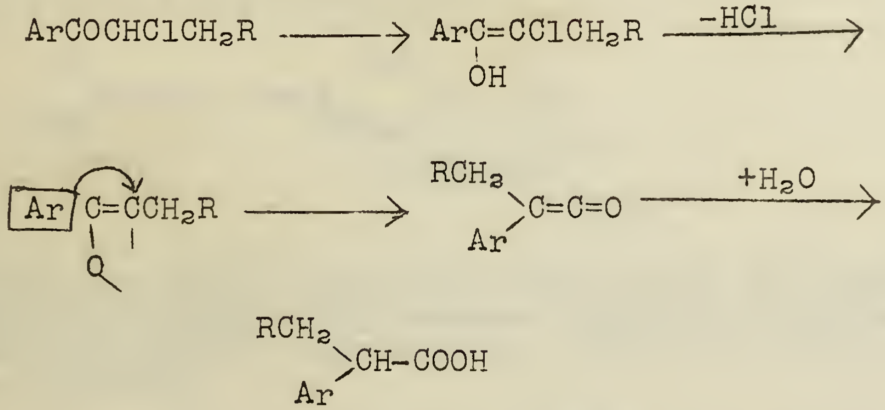
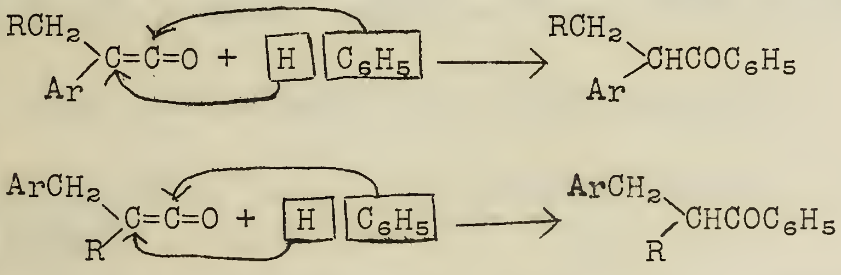


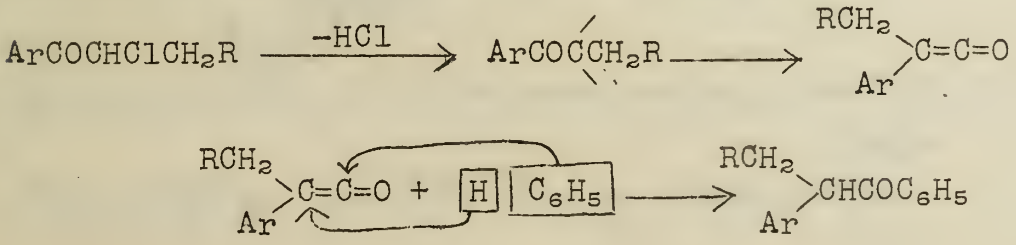
The ketones $ArCOCHClCH_2R$ which give only the vinyl halide type enol yielded the acid $RCH_2CH(Ar)COOH$ which can be explained by a similar mechanism.



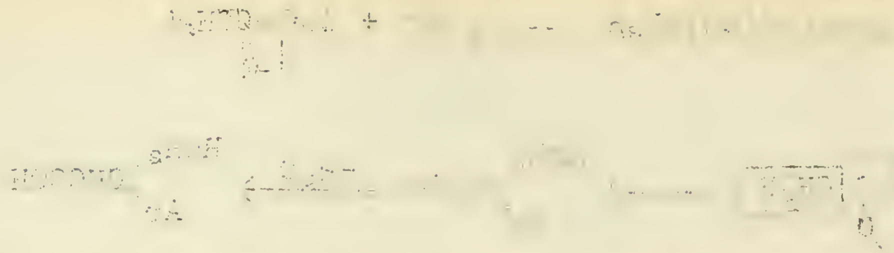
That these ketenes are not involved in the reactions of the ketones $ArCHClCOCH_2R$ and $ArCH_2COCHClR$ with benzene in the presence of aluminum chloride is evident because addition of benzene to the ketenes would form $RCH_2CHArCOC_6H_5$ and $ArCH_2CHRCOC_6H_5$ respectively.



However, in cases where the ketones $ArCOCHClCH_2R$ did react, the product isolated was not $ArCOCH(C_6H_5)CH_2R$ which should be formed by direct substitution of the phenyl radical for the chlorine atom but $RCH_2CH(Ar)COC_6H_5$ which could be obtained by addition of benzene to the ketene.



The ketones $ArCHClCOCH_2R$ are readily hydrolyzed in the presence of sodium carbonate to hydroxy ketones and they react with sodium phenolate to form phenyl ethers. The ketones $ArCOCHClCH_2R$ are



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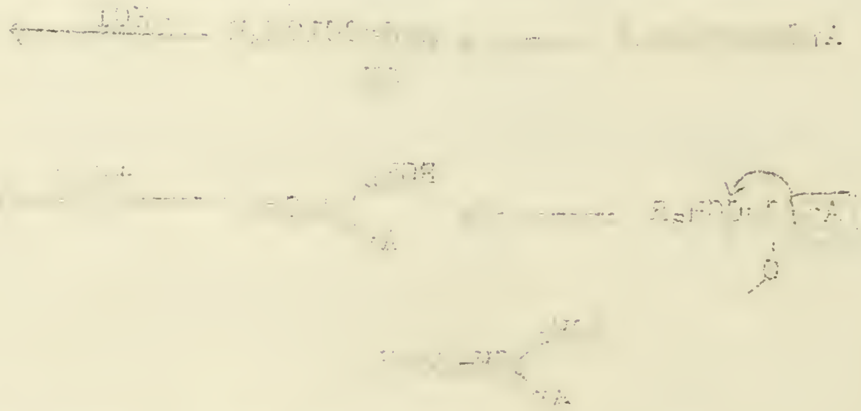


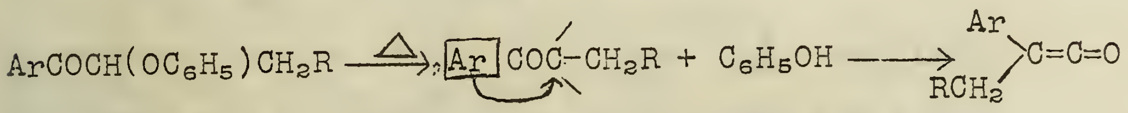
[illegible]

[illegible]

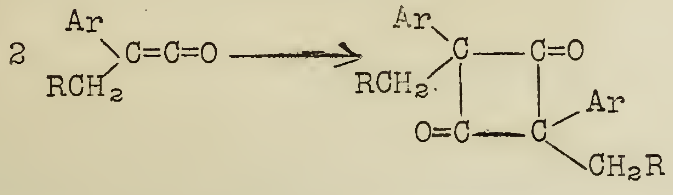
[illegible]

difficultly hydrolyzed and only in a few cases was any reaction obtained with sodium phenolate.

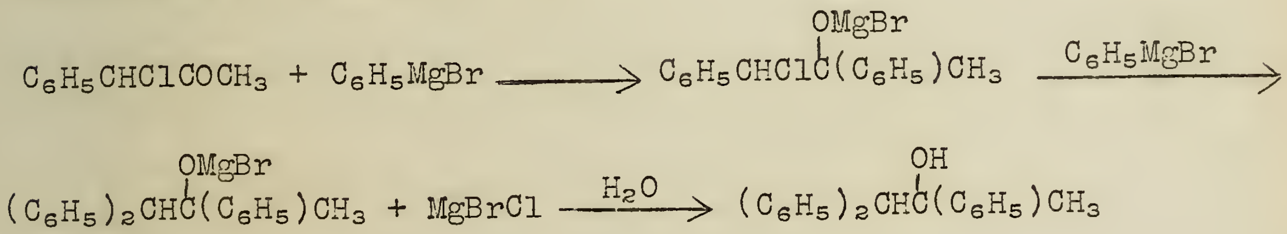
The pyrolysis of the phenyl ethers thus obtained was interesting because substituted cyclobutanediones were formed.



The ketene thus formed dimerizes.



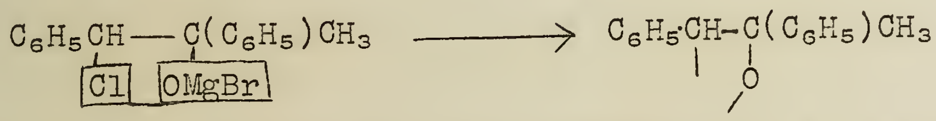
The reaction of phenyl magnesium bromide with the ketones $C_6H_5COCHClC_6H_5$ and $C_6H_5CHClCOCH_3$ produced $(C_6H_5)_2C(OH)CH(C_6H_5)_2$ and $(C_6H_5)_2CHC(OH)(C_6H_5)CH_3$ respectively. With the second, two mechanisms are possible.



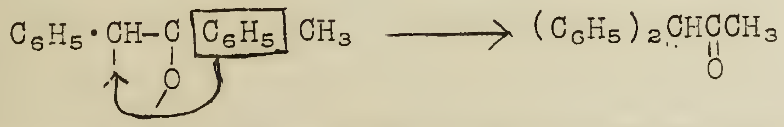
$$C_6H_5CHClCOCH_3 + C_6H_5MgBr \longrightarrow C_6H_5CHCl\overset{OMgBr}{C}(C_6H_5)CH_3 \xrightarrow{C_6H_5MgBr}$$

$$(C_6H_5)_2CH\overset{OMgBr}{C}(C_6H_5)CH_3 + MgBrCl \xrightarrow{H_2O} (C_6H_5)_2CH\overset{OH}{C}(C_6H_5)CH_3$$

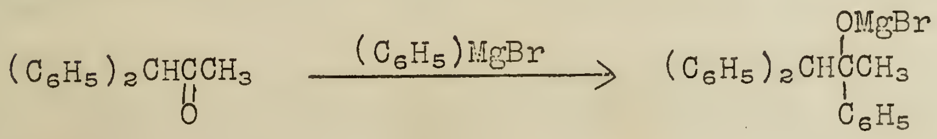
The MgBrCl could also be split out intramolecularly.



The divalent radical thus formed rearranges to a ketone by a mechanism similar to that which Tiffeneau calls the semipinacol rearrangement.



The second mole of the Grignard reagent then adds to this ketone.



$$(C_6H_5)_2CH\underset{\overset{\|}{O}}{C}CH_3 \xrightarrow{(C_6H_5)MgBr} (C_6H_5)_2CH\underset{C_6H_5}{\overset{OMgBr}{C}}CH_3$$

The intermediate ketone $(C_6H_5)_2CHCOCH_3$ was isolated, indicating that the second mechanism is most plausible.

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Neff, Ann., 335, 263 (1904)
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Pdrost and Kinmann, Bull. soc. chim., 49, 194 (1931)
Kinmann, Ann. chim., 11, 223 (1929)
Tiffeneau and Tchoubar, Comp. rend., 198, 941 (1934)
Tiffeneau, Bull. soc. chim., 49, 1692 (1931)

Reported by E. H. Dobratz
October 26, 1938

SYNTHESIS OF POLYENES FROM ACETYLENE AND DIACETYLENE

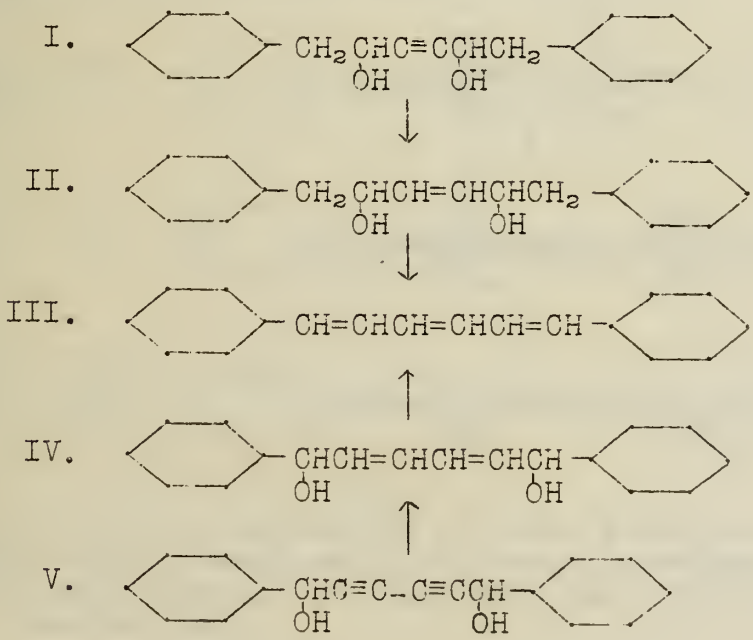
Kuhn and Wallenfels -- Kaiser Wilhelm Institute, Heidelberg

In 1913, G. Dupont discovered that acetylene-dimagnesium bromide would react with aldehydes and ketones to give acetylene glycols. Similarly, it was reported by Straus (1930) that diacetylene-dimagnesium bromide could be used to prepare the corresponding diacetylene glycols. By catalytic half-hydrogenation of these substances they may be converted into ethylene glycols. Finally, the hydroxyl groups can be removed by treatment with P_2I_4, VCl_2 or $CrCl_2$ to give polyenes.

I. Diphenylpolyenes.

Application of the method to phenylacetaldehyde and acetylene gave compound I. Hydrogenation of this substance (1 mole) yielded compound II, and by warming this compound with acetic anhydride and $KHSO_4$ two molecules of water were split out to give the hydrocarbon (III).

The same triene can be obtained from diacetylene by treating the Grignard compound with two moles of benzaldehyde to give the diol (V). The hydrocarbon is obtained by hydrogenation (2 moles) and subsequent treatment with P_2I_4.

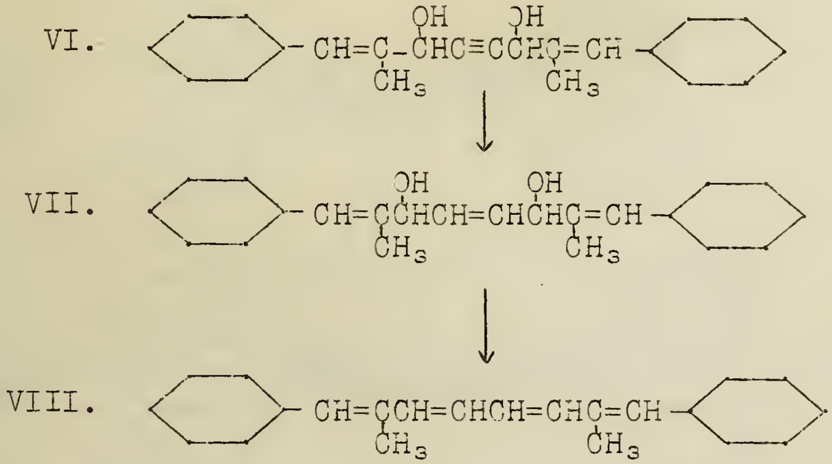


Several of these compounds exhibit possible isomers but only in a few cases was separation accomplished. Because the separations were attempted in all cases, the yields reported are considerably lower than could be expected if the reactions were run with the single purpose of obtaining the polyenes.

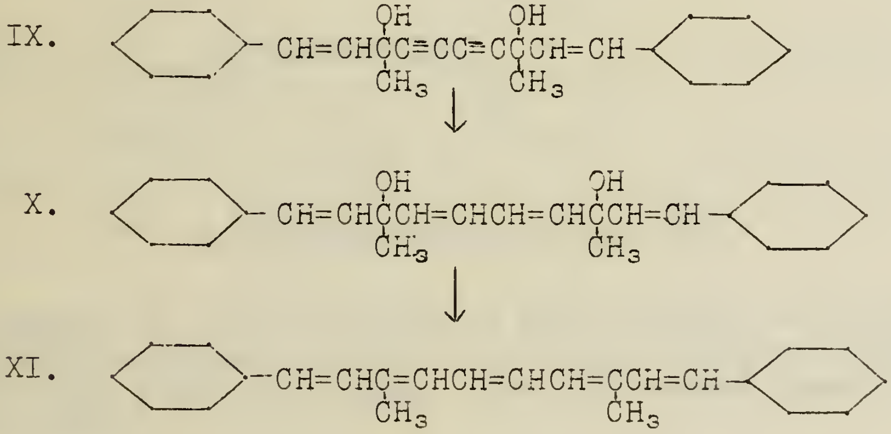
II. Diphenylpolyenes with Branched-chain Methyl Groups.

Using acetylene and diacetylene it is possible to prepare methylated diphenylpolyenes which could not be obtained by the methods previously described by Kuhn and coworkers.

α-Methyl cinnamic aldehyde and acetylene were used to obtain the 1,8-diphenyl-2,7-dimethyl-octatetraene as follows:


VI.
CH=C-CHC≡CCHC=CH
OH
OH
CH3
CH3
VII.
CH=CCHCH=CHCHC=CH
OH
OH
CH3
CH3
VIII.
CH=CCH=CHCH=CHC=CH
CH3
CH3

In the same way 1,10-diphenyl-3,8-dimethyl-decapentaene was obtained from benzalacetone and diacetylene


IX.
CH=CHCC≡CC≡CCCH=CH
OH
OH
CH3
CH3
X.
CH=CHCCH=CHCH=CHCCH=CH
OH
OH
CH3
CH3
XI.
CH=CHC=CHCH=CHCH=CCH=CH
CH3
CH3

Compound XI is noteworthy, since, with its uneven number of conjugated double bonds and symmetrical arrangement of twelve aliphatic carbon atoms, it resembles the middle portion of the natural carotinoids.

Absorption studies were made to indicate the effect of the methyl groups. The band of largest wave length lies at 437 $m\mu$ for 1,10-diphenyl-3,8-dimethyl-decapentaene; that for 1,10-diphenyl-decapentaene lies at 436 $m\mu$. The two methyl groups have, therefore, shifted the band 11 $m\mu$ toward the red.

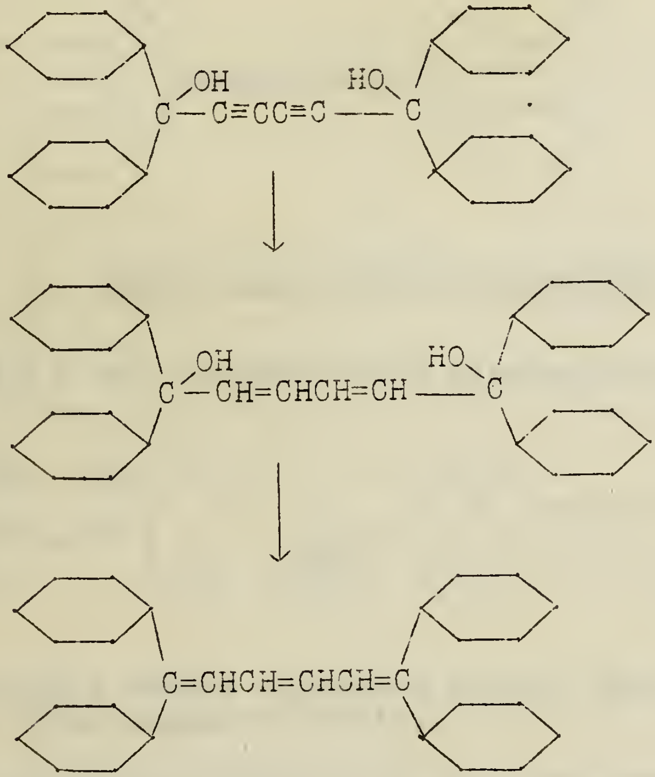
III. Tetraphenylpolyenes.

1,1,6,6-Tetraphenylhexatriene, first prepared by Wittig and Klein from the dimethyl ester of α,α'-dihydromuconic acid and phenyllithium, can be prepared using diacetylene and benzophenone.

XII.

XIII.

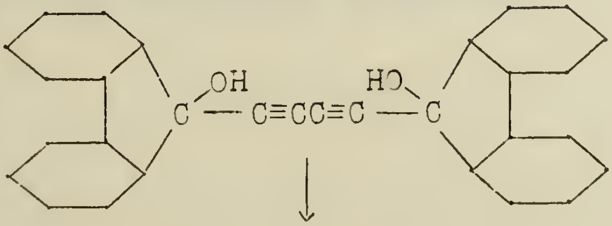
XIV.

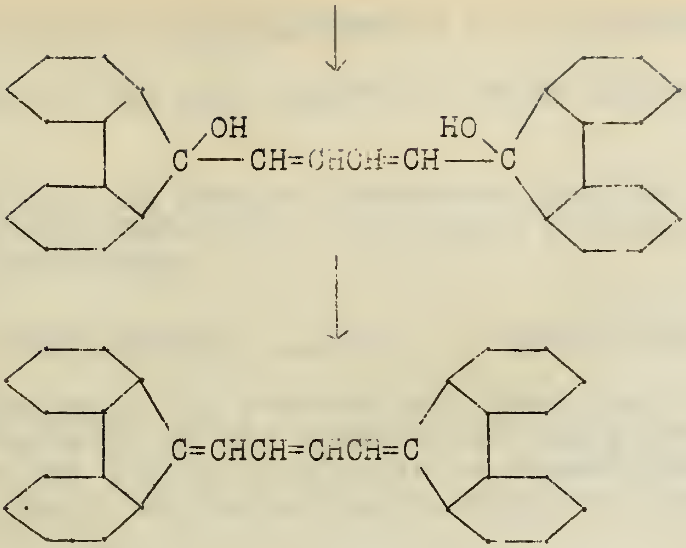

OH
HO
C—C≡CC≡C——C
OH
HO
C—CH=CHCH=CH——C
C=CHCH=CHCH=C

IV. 1,6-Dibiphenylene Hexatriene.

This example of the fluor-series had already been prepared by Kuhn and Winterstein in a yield of 2.1 per cent by treating dihydromuconic acid with fluorenone. The new method gave yields of about 25 per cent.

XV.


OH
HO
C—C≡CC≡C—C



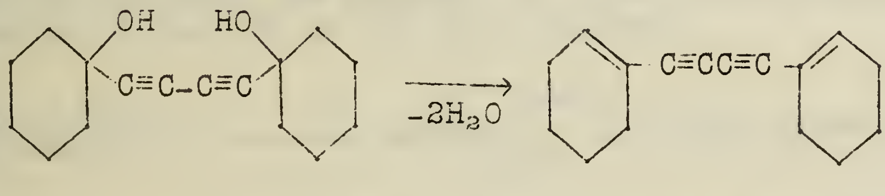
XVI.

XVII.

V. Di(△'-cyclohexenyl)-butadiyne.

Compound XVIII was prepared from diacetylene and cyclohexanone as follows:

XVIII.



XIX.

The hydrocarbon formed colorless prisms which changed to a gold color upon long exposure to air.

Di-(△'-cyclohexenyl)-acetylene has been prepared by Pinckney, Nesty and Marvel by a corresponding manner from cyclohexanone and acetylene.

Bibliography:

Kuhn and Wallenfels, Ber. 71, 1889 (1938).

This article gives 14 additional references.

Reported by R. V. Lindsey, Jr.
November 2, 1938

HYDROBENZOINIC REARRANGEMENTS WITH REPLACEMENT OF ONE OR TWO ARYL GROUPS BY OTHER RADICALS

In 1875 Zincke and Breuer discovered that the symmetrical diaryl glycols ArCHOHCHOHAr' are transformed by simple dehydration into diarylacetaldehydes.

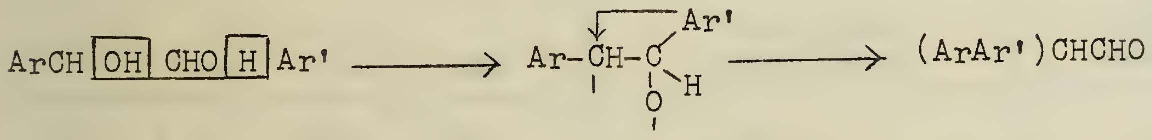
$$\mathrm{ArCHOHCHOHAr'} \xrightarrow{-H_2O} (\mathrm{ArAr'})\mathrm{CHCHO}$$

Tiffeneau investigated the problem and found that this rearrangement is characteristic of the symmetrical diaryl α-glycols. It is not produced in the dialkyl α-glycols or symmetrical aryl-alkyl glycols, which yield the unrearranged ketone by dehydration.

$$\mathrm{RCHOHCHOHR'} \xrightarrow{-H_2O} \mathrm{RCH_2COR'}$$

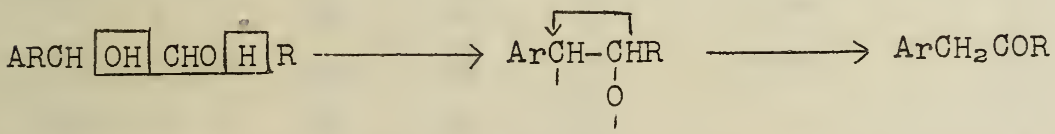
$$\mathrm{ArCHOHCHOHR} \xrightarrow{-H_2O} \mathrm{ArCH_2COR}$$

The mechanism of the hydrobenzoinic rearrangement is explained by Tiffeneau by two distinct steps: the elimination of one of the hydroxyl groups with the hydrogen of the other hydroxyl group, then preferential migration of the aryl radical:



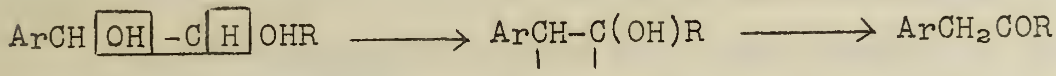
$$\mathrm{ArCH}\boxed{\mathrm{OH}}\,\mathrm{CHO}\boxed{\mathrm{H}}\,\mathrm{Ar'} \longrightarrow \mathrm{Ar{-}\underset{|}{C}H{-}\underset{\underset{|}{O}}{\overset{Ar'}{C}}{-}H} \longrightarrow (\mathrm{ArAr'})\mathrm{CHCHO}$$

The difference between the dialkyl glycols, the alkyl-aryl glycols, and the diaryl glycols lies in the second step. With the first two groups the dehydration is followed by migration of the hydrogen atom adjacent to the alkyl radical.



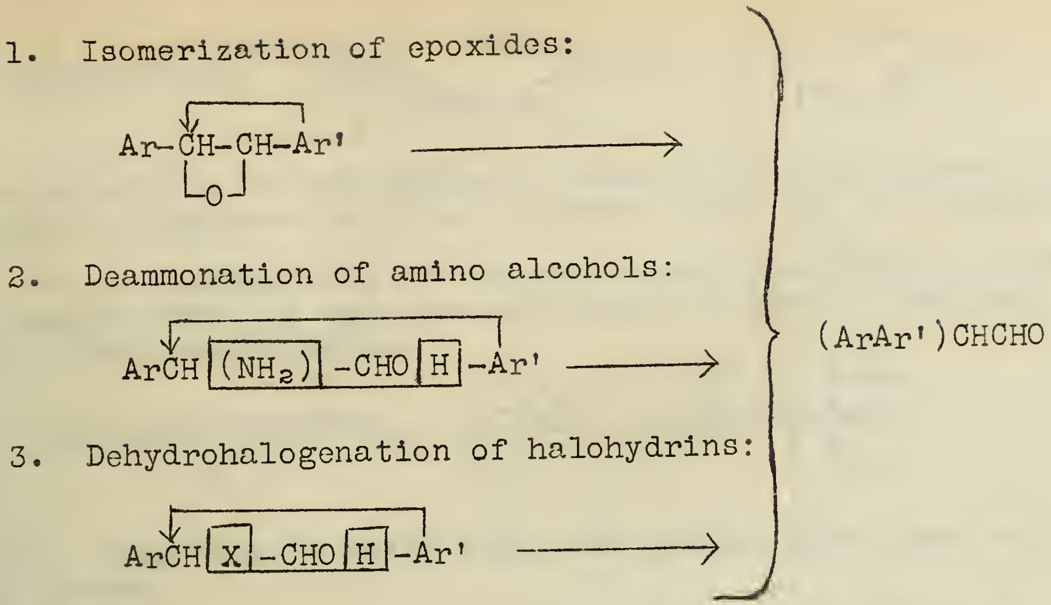
$$\mathrm{ARCH}\boxed{\mathrm{OH}}\,\mathrm{CHO}\boxed{\mathrm{H}}\,\mathrm{R} \longrightarrow \mathrm{Ar\underset{|}{C}H{-}\underset{\underset{|}{O}}{C}HR} \longrightarrow \mathrm{ArCH_2COR}$$

A second possibility for this last group is a vinyl dehydration, in which one of the hydroxyl groups (always that nearest to the aryl group present) is eliminated with the non-hydroxyl hydrogen of the adjacent carbon atom, followed by the obligatory migration of the hydrogen of the vinyl hydroxyl group:



$$\mathrm{ArCH}\boxed{\mathrm{OH}}{-}\mathrm{C}\boxed{\mathrm{H}}\,\mathrm{OHR} \longrightarrow \mathrm{Ar\underset{|}{C}H{-}\underset{|}{C}(OH)R} \longrightarrow \mathrm{ArCH_2COR}$$

In the course of their extensive investigations, Tiffeneau and his coworkers have also studied three other reactions which are capable of undergoing the same hydrobenzoinic rearrangement. These are as follows:



1. Isomerization of epoxides:

$$Ar-\overset{\downarrow}{C}H-CH-Ar' \underset{O}{\sqcup} \longrightarrow$$

2. Deammonation of amino alcohols:

$$Ar\overset{\downarrow}{C}H\boxed{(NH_2)}-CHO\boxed{H}-Ar' \longrightarrow$$

3. Dehydrohalogenation of halohydrins:

$$Ar\overset{\downarrow}{C}H\boxed{X}-CHO\boxed{H}-Ar' \longrightarrow$$

$(ArAr')CHCHO$

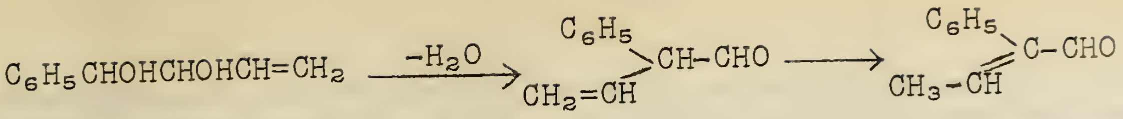
Of these three reactions, only the last has not been fully realized, due to the difficulty of attaching HOI to the ethylenic compounds $ArCH{=}CHAr'$; moreover, the iodohydrins so obtained lose HOI and not HI. Some of the results obtained from (I) dehydration of glycols, (II) deammonation of amino alcohols, and (III) isomerization of epoxides, are as follows:

		Ar	Ar'	Aldehydes $(ArAr')CHCHO$	Ketone $ArCH_2COAr'$ or $ArCOCH_2Ar'$
I.	1	Ph	Ph	+++	+
	2	Ph	Pip	+	+++
	3	Ph	Tol	++++	–
	4	Ph	An	++++	–
	5	An	An	++++	–
II.	6	Ph	Ph	–	++++
	7	o-An	o-An	++++	–
III.	8	Ph	p-Tol	++++	–
	9	Ph	Pip	+	+++

These four reactions also have been studied in the following series of compounds:

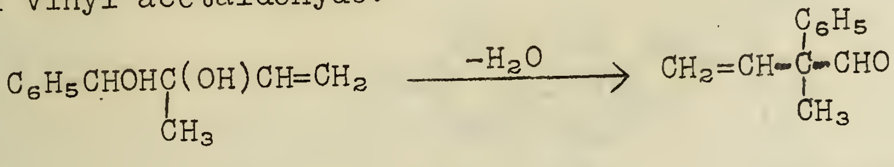
I. Compounds in which one aryl group has been replaced by a vinyl radical.

A. Dehydration of phenylvinyl glycol yielded α-phenylcrotonaldehyde exclusively.



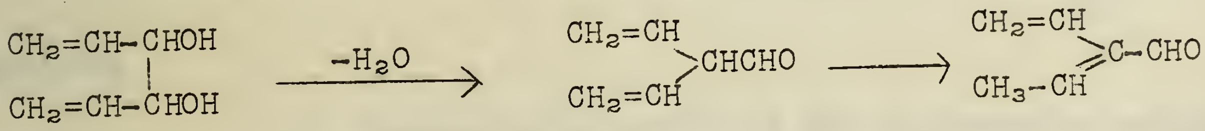
It is impossible to say whether a phenyl or a vinyl group migrated. Evidently a hydrogen has also migrated after the rearrangement.

B. Dehydration of 1-phenyl-2-methyl-2-vinyl glycol and the isomerization of the corresponding epoxide yielded only phenyl methyl vinyl acetaldehyde.



II. Compounds in which both aryl groups have been replaced by vinyl groups.

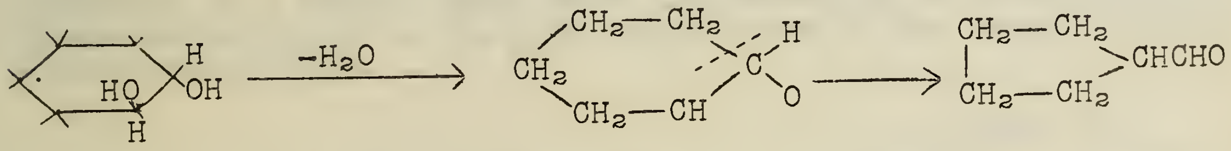
The dehydration of divinyl glycol with hot 50 per cent sulfuric acid yielded α-phenylcrotonaldehyde by hydrobenzoinic rearrangement, followed by migration of a double bond.



III. Compounds in which the two aryl groups are replaced by the methylene groups of a cyclane.

A. Bisecondary cyclanediols.

The dehydration of trans-cyclohexanediol, the dehydrohalogenation of the corresponding chlorohydrin, and the deammonation of the corresponding amino alcohol yielded cyclopentyl formaldehyde by hydrobenzoinic rearrangement.

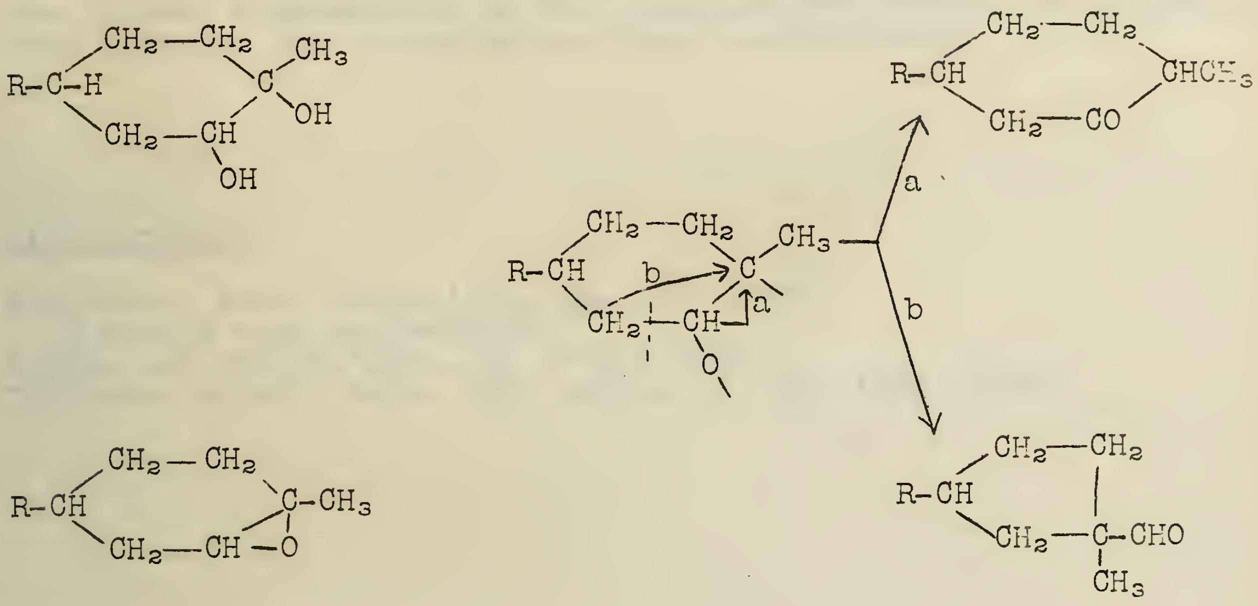


Dehydration of the cis-cyclohexanediol and dehydrohalogenation of the corresponding chlorohydrin yielded cyclohexanone, apparently by a vinyl dehydration. Strangely enough, the isomerization of cyclohexeneoxide, which can exist only in the cis-form, yielded cyclopentyl formaldehyde exclusively.

B. Semihydrobenzoinic rearrangements by the dehydration of secondary-tertiary cyclanic diols and isomerization of the corresponding epoxides; semipinacolic rearrangements by the dehydrohalogenation of their halohydrins and the deammonation of their amino alcohols.

1. The dehydration of 1-methyl-cyclohexanediol and isomerization of the corresponding epoxide furnished, along with the predominating methyl cyclohexanone arising from a

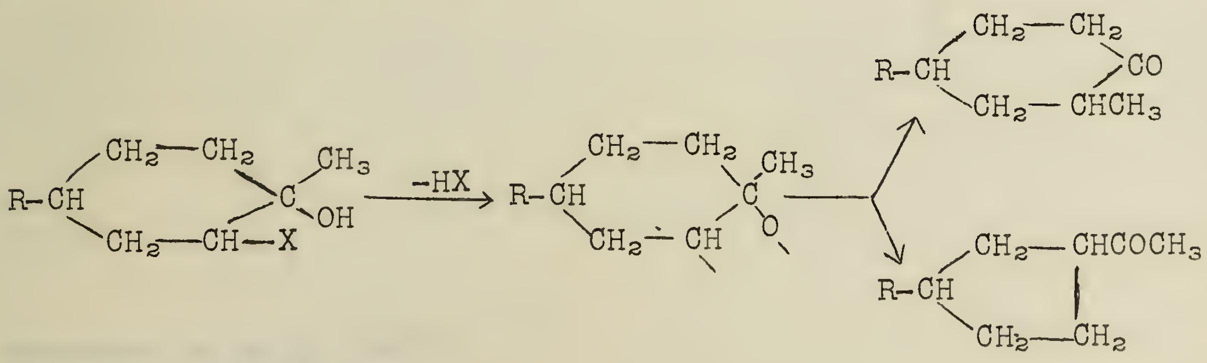
semipinacolic rearrangement, a small quantity of methyl cyclopentyl formaldehyde resulting from a semihydrobenzoinic rearrangement.



R=H, CH_3

2. Dehydrohalogenation of the halohydrins and deammonation of the amino alcohols corresponding to the above glycols.

The course of these reactions depends on the relative positions of the hydroxyl and halogen (or amino) groups. Only when the hydroxyl is secondary can the intermediate formed lead to a semihydrobenzoinic rearrangement. However, the difficulties of obtaining such compounds have not allowed these reactions to be carried out yet. The compounds with a tertiary hydroxyl group are easily obtained. Upon dehydrohalogenation there is produced a semipinacolic rearrangement permitting a double migration: 1) the migration of a methyl group with the formation of a cyclohexanone; 2) the migration of a CH_2 with contraction of the ring, forming acetylcyclopentane.



R=CH_3 or H; X=Cl, I, or NH_2

The nitrous deammonation of the corresponding amino alcohols yielded both ketones, the acetylcyclopentane predominating.

Bibliography:

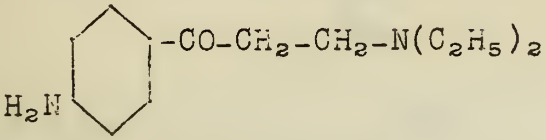
Tiffeneau, Helv. Chim. Acta, 21, 404 (1938)
(a review with references)
Zincke and Breuer, Ber., 9, 1769 (1876)
Tiffeneau et al., Bull. soc. chim., (4) 49, 1595 (1931)

Reported by S. L. Scott
November 2, 1938

ANESTHETIC EFFECT OF 2-ALKOXY QUINOLINES

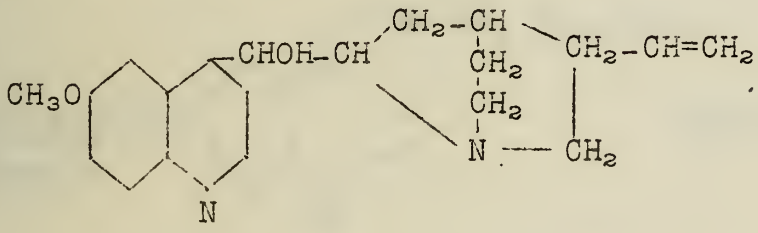
H. Wojahn -- Pharmaceutical Institute of the University of Kiel

Since the discovery of cocaine over one hundred years ago chemists have been striving to make better local anesthetics. Of the more successful type prepared was novocaine



which was found to be less active, but superior to cocaine in that the former was less habit forming.

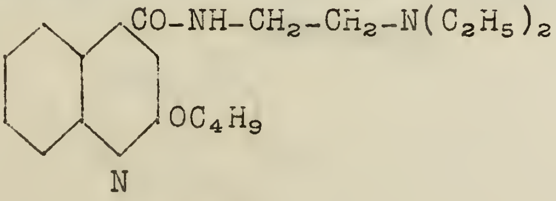
It has been known for many years that quinine (I) in addition to being an anti-malarial, was also a local anesthetic



I

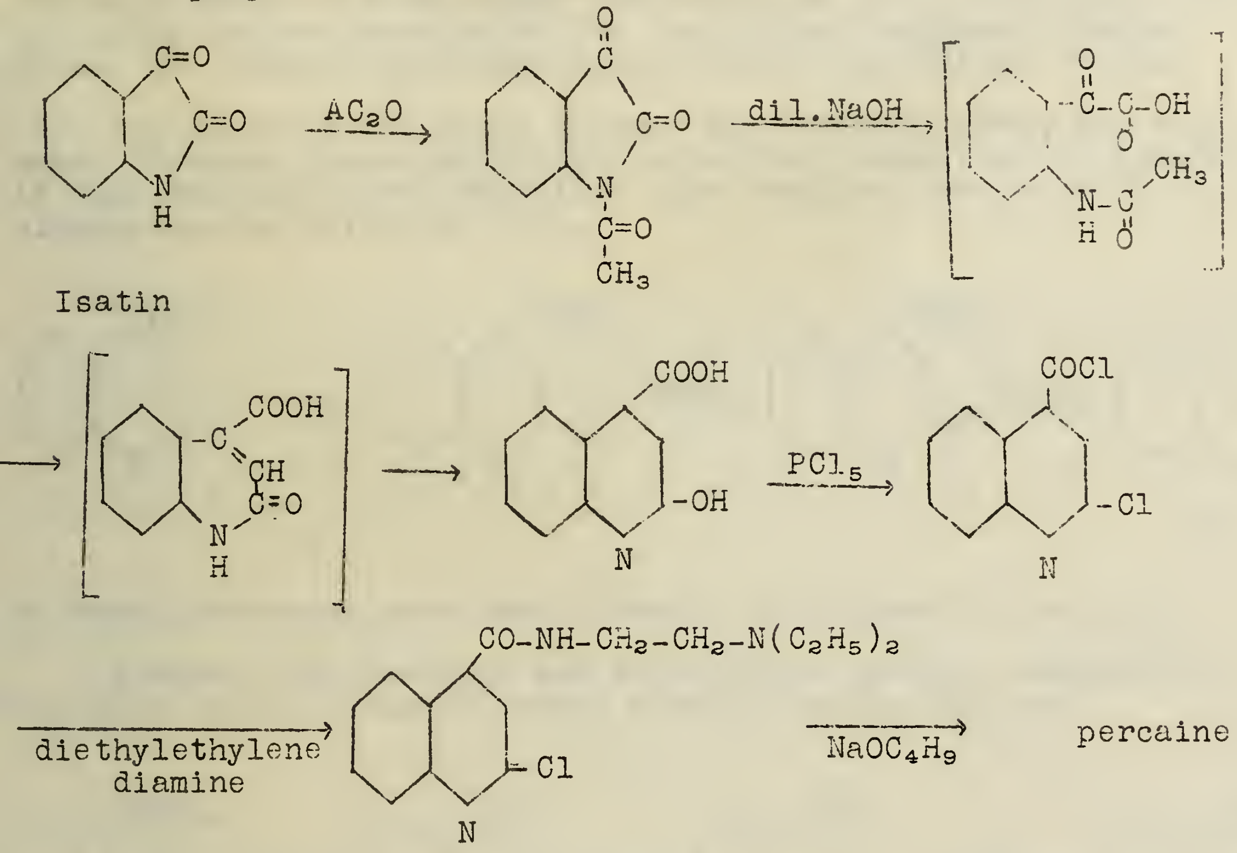
In 1927 Miescher made a series of local anesthetics which were a combination of the above two types. The most effective one of the series was percaine (II), which was found to be forty times as active as novocaine and twenty times as active as cocaine. Although its effect lasted six to ten hours, it was five times as toxic as cocaine.

The success of percaine in its medicinal use has led to the opening of an entirely new field of local anesthetics. Miescher found that the butyloxy group was



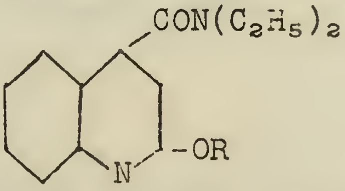
II

most effective and the increasing or decreasing of the size of the alkoxy group resulted in a lowering of the anesthetic action. Percaine is prepared commercially as follows:


Isatin
AC_2O
dil. NaOH
PCl_5
diethylethylene diamine
$NaOC_4H_9$
percaine
COOH
-OH
COCl
-Cl
$CO-NH-CH_2-CH_2-N(C_2H_5)_2$

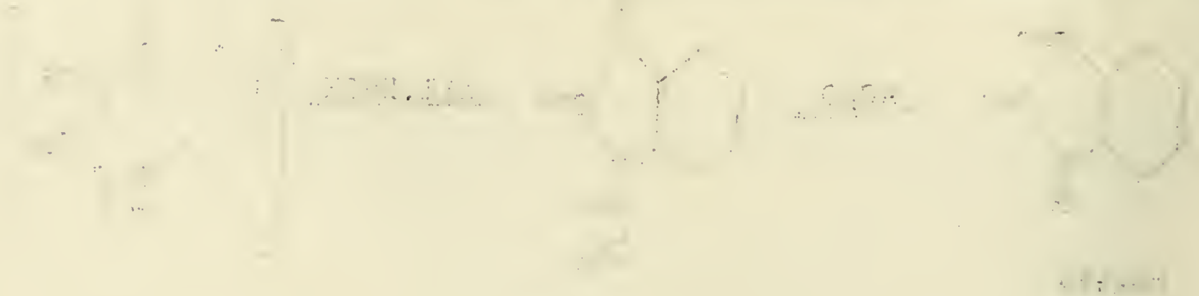
Wojahn undertook a systematic study to determine which groups in percaine were necessary to give local anesthesia. That an alkoxy group is necessary is revealed by quinine which is active and cinchonine, the quinine compound without the methoxyl, which is inactive. The synthesis and action of percaine has shown that the alkoxy group in the 2-position of the quinoline ring gives an increased effect over that of the 6-position in quinine.

By observing which types of compounds exhibit local anesthesia, it has been found that they are all strongly basic and have a high lipoid solubility. The latter is to be expected as the nerve tissue is known to have a high fat content. For example the diethylamide of 2-alkoxy cinchoninic acid (III) has a high lipoid solubility

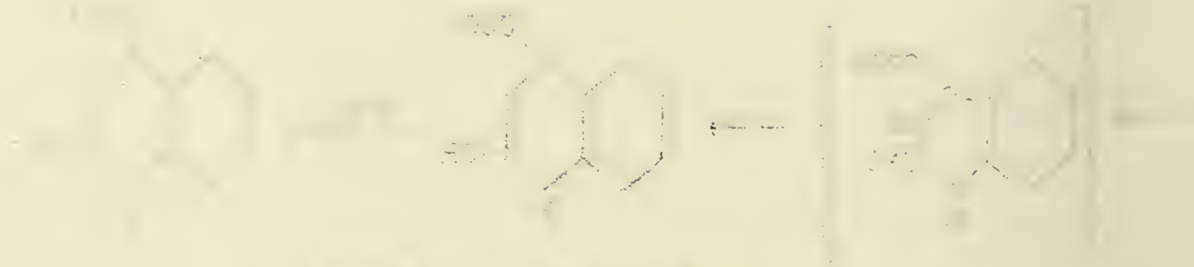

$CON(C_2H_5)_2$
-OR
N

III

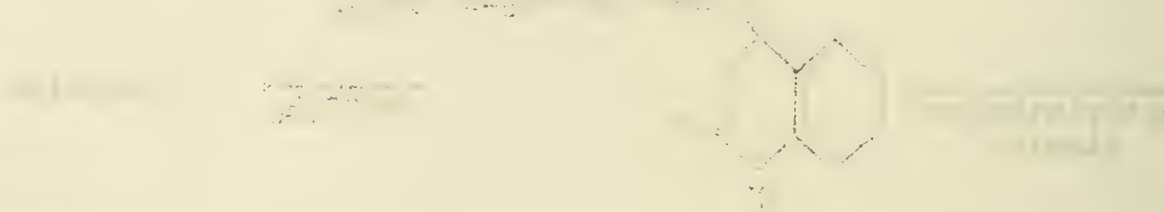
most active and the increasing or decreasing of the size of the alkoxy group resulted in a lowering of the anesthetic action. [illegible] is prepared commercially as follows:



[illegible]

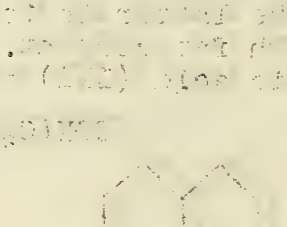


[illegible]



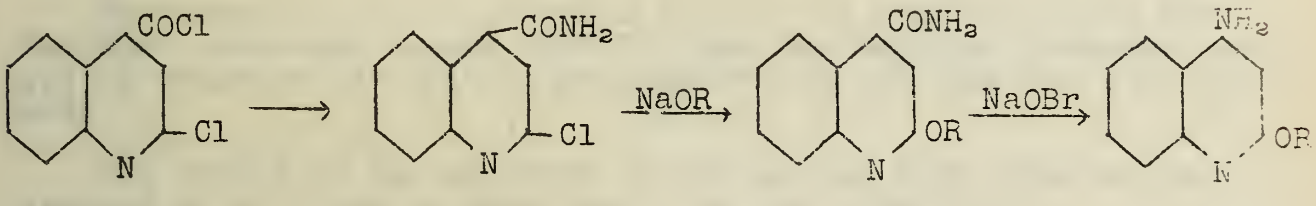
[illegible] alkoxy group [illegible]

It was found [illegible] which type of [illegible] that the alkoxy [illegible] This appears to be [illegible] acid (C?) [illegible]



but a low basicity and has little anesthetic action. However, the diethylamino ethanol ester has a high lipoid solubility, is strongly basic, and is a good anesthetic. As the diethylamino ethanol group can be substituted for the diethyl ethylene diamine group, the latter is not necessary for the anesthetic action.

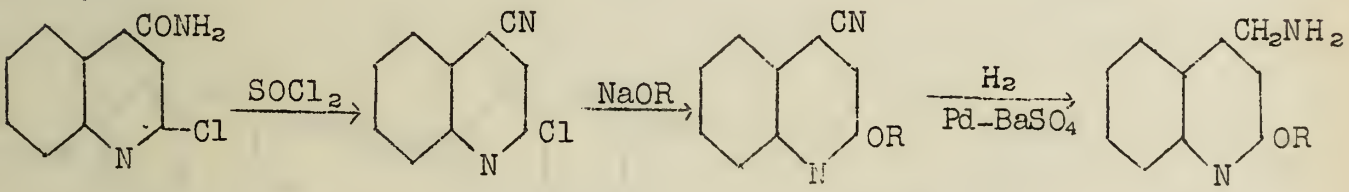
The question now arose whether the carboxyl group was necessary. Perhaps other derivatives of alkoxy quinoline would work if they had sufficient basicity. The simplest case would be 2-alkoxy-4-amino quinoline (IV).


COCl
Cl
N
CONH2
Cl
N
NaOR
CONH2
OR
N
NaOBr
NH2
OR
N

IV

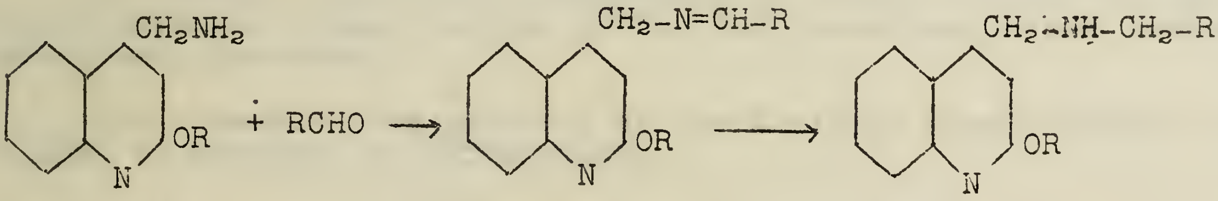
As these compounds were weakly basic, they showed no activity.

However, the basicity and activity are greatly enhanced if the amino group is not attached directly to the nucleus.


CONH2
Cl
N
SOCl2
CN
Cl
N
NaOR
CN
OR
N
H2
Pd-BaSO4
CH2NH2
OR
N

V

The effect of substitution on the 4-aminomethyl group was carried out and the compounds obtained were too weakly basic to have anesthetic action


CH2NH2
OR
N
+ RCHO
CH2-N=CH-R
OR
N
CH2-NH-CH2-R
OR
N

VI

Three basic groups in the molecule as exemplified by VII lead to compounds of no action

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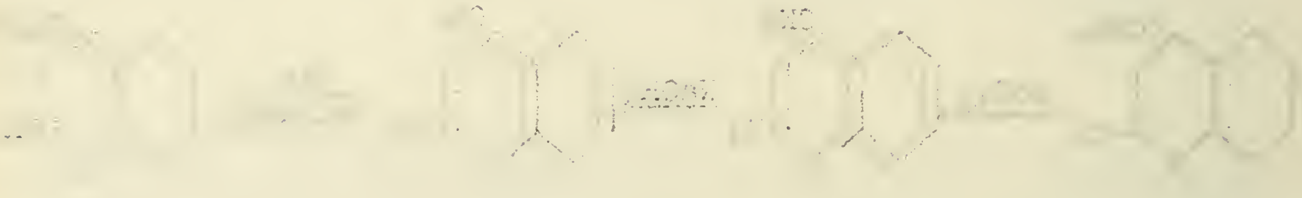
[illegible]

[illegible]

[illegible]



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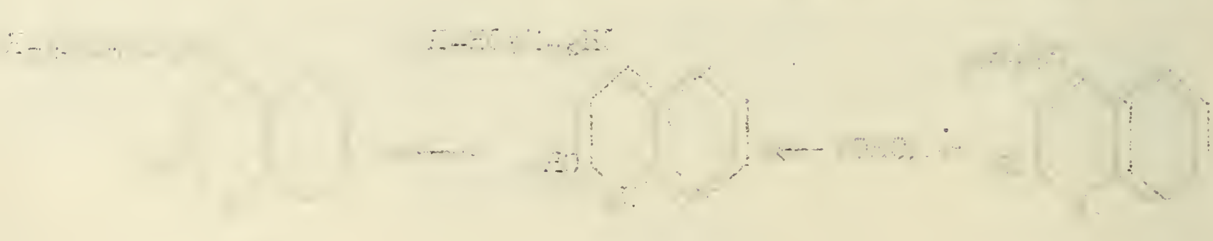

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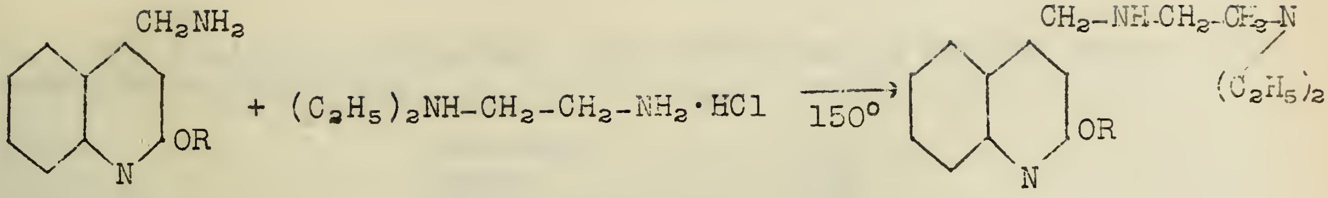
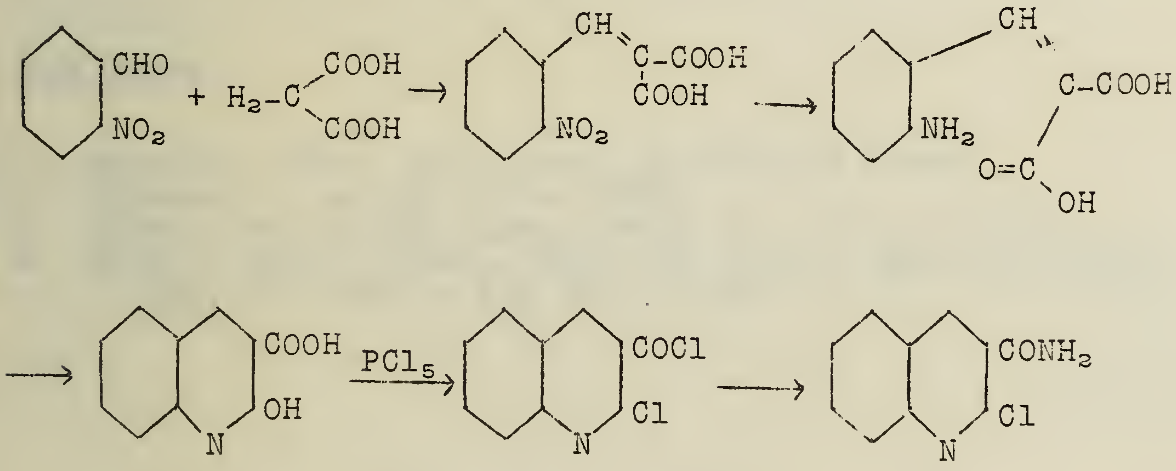


VII

By comparing VII to percaine (II) it is seen that both have identical structure except that VII has the carbonyl reduced. This type of compound had a low lipoid solubility and was too strongly basic.

The effect of the position of the aminomethyl group was determined by shifting it from the 4- to the 3-position.

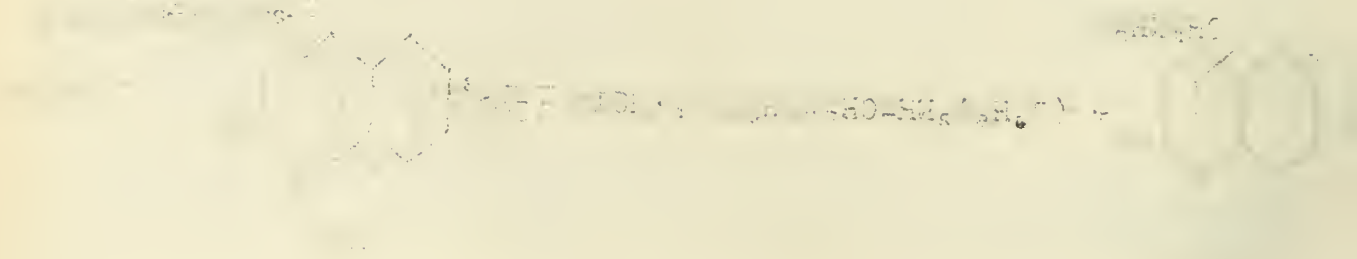


These compounds had almost the same action strength as the 4-aminomethyl quinolines.

To further check the independence of change of position the 2-diethylamino ethanol esters of the 2-alkoxy-3-quinoline carboxylic acids were prepared.

The comparison of activity of the 2-alkoxy-4-aminomethyl quinolines to percaine is interesting.

Percaine	1.00	isopropyloxy	0.49
methoxy	0.10	butyloxy	1.37
ethoxy	.49	isobutyloxy	1.17
propyloxy	1.17	sec.-butyloxy	0.58
isoamyloxy	2.60		



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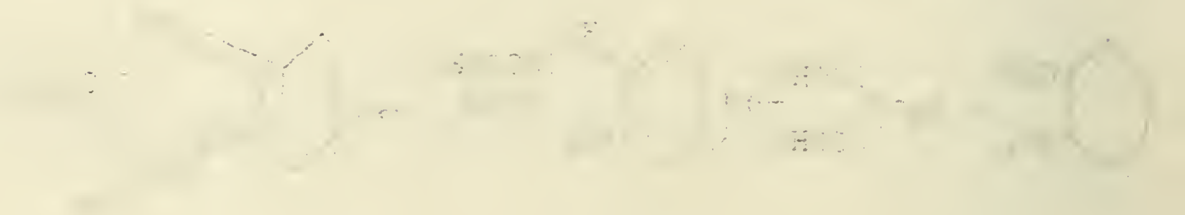

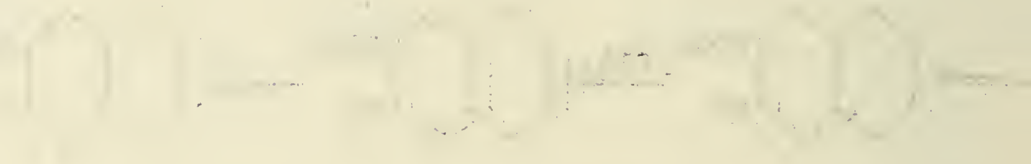

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The 2-alkoxy-cinchoninic acid diethylamino ethanol esters were compared to novocaine.

novocaine	1.00
ethoxy	0.39
propyloxy	.48
isopropyloxy	.33
butyloxy	3.30

The conclusion concerning the effective groups of percaine is thus shown that the 2-alkoxy quinoline is most important and in order to be a local anesthetic needs only an additional group of the correct basicity.

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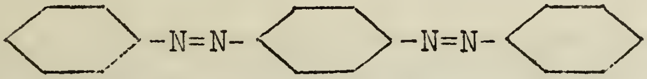
Reported by B. R. Baker
November 9, 1938

POLYAZOBENZENES

Ruggli and Petitjean -- University of Basel

The method for making azo substances, employing aromatic nitroso compounds and aromatic amines, is seldom used. However, Ruggli's present work is concerned, primarily, with these nitroso methods, connecting more than two phenyl nuclei through an azo group in the para position. Colored substances were formed which might be considered to be azo-homologs of azobenzene with a respective increase of -N=N-⬡, the para series being called, for short, "polyazobenzenes." The next homolog after azobenzene will be called, accordingly, disazobenzene.

It is difficult to push the coupling of three aniline nuclei. Nietzki and Diesterweg coupled diazotized aminoazobenzene with aniline and obtained a diazoamino substance, from which the desired aminodisazobenzene was prepared, (in 1 per cent yield), by heating with aniline hydrochloride. This, when diazotized and decomposed by refluxing with alcohol, yielded a yellow-red substance which melted at 98° and was pronounced disazobenzene, on the basis of the analysis.



Later, this compound was shown not to be identical with p-disazobenzene prepared in another, more satisfactory way. Its structure is, therefore, equivocal, the two compounds probably being isomers. The true p-disazobenzene was prepared by Mills, and recently thereafter by Bamberger and Busdorf, from p-aminoazobenzene and nitrosobenzene, as bright, orange-yellow leaflets with an intensive bronze sheen, (m.p. 167°) Ruggli prepared the substance in the same way, with 87 per cent yield.

A reduction was carried out to obtain, if possible, dishydrazobenzene and hydrazoazobenzene, which compounds should undergo interesting benzidine rearrangements. The reduction was performed catalytically with nickel and was so conducted that the hydrogen taken up could be determined. The reaction was run first, with the calculated four atoms of hydrogen, to obtain the first mentioned product above, but, instead, hydrazoazobenzene was isolated in 21 per cent yield. By using two atoms of hydrogen the yield was increased to 47 per cent. On this and later work is established the fact that, in general, dishydrazobenzenes are not stable but, in the hydrogenation, hydrazoazobenzenes will split across the hydrazo-bond. The products are isolated in the form of their acetyl derivatives. Hydrolysis of the latter must be carried out under nitrogen, as the free hydrazoazobenzenes are easily dehydrogenated in the air.

Treatment with hydrochloric acid gave a brick-red substance of the formula $C_{18}H_{12}N_4Cl_2$ and having a melting point of 263-264°. Evaporation of the filtrate gave the hydrochloride of a basic sub-

stance in very small amount. This was isolated and purified as the benzoyl derivative, (m.p. 208°). The latter has the formula $C_{25}H_{20}N_4O$ and is thus isomeric with a monobenzoylhydrazoazobenzene. The possibility of a benzidine rearrangement is discussed.

Following the disazobenzenes are the next homologs, the trisazobenzenes, first prepared by Valori by oxidation of aminoazobenzene with 30 per cent H_2O_2 in acetic acid. Ruggli used p-p'-diaminoazobenzene and 2 mols of nitrosobenzene, the product crystallizing in copper-red leaflets.

Another method of preparing polyazo substances was by the use of p-dinitrosobenzene. The condensation of such compounds with aniline gives, not without other things, the desired disazobenzenes but the course is indirect. By warming with alcohol, which contains some glacial acetic acid, a yellow-orange substance is formed, ($C_{18}H_{14}N_4O$) which is distinguished from disazobenzene by the oxygen content. It is proposed to be the yet unknown azoazoxybenzene. Hydrogen peroxide in acetic acid oxidized it to disazoxybenzene.

By condensation of dinitrosobenzene with aminoazobenzene, a mixture of trisazoazoxybenzene and tetrakisazobenzene is formed, which, on account of its insolubility in pyridin, is not easily reduced to the pure azo substance. The latter is made by another method.

The reaction of dinitrosobenzene with p-aminoacetanilide yields, by a reaction on one side of the molecule, an azo-, on the other side, an azoxy-condensation, to give reddish brown diacetaminoazoazoxybenzene. This may be hydrolyzed to the free diaminoazoazoxy compound which is sufficiently soluble in cold pyridine for a catalytic elimination of oxygen to be effected. In the presence of acetic anhydride the product is diacetaminodisazobenzene, which may be hydrolyzed to the free diamine. Condensation with two molecules of nitrosobenzene gives pure tetrakisazobenzene.

Many attempts were made to prepare hexakisazo substances, using diaminotetrakisazobenzene, but the products were of doubtful composition and all had high decomposition points. Several attempts to make pentakisazobenzene all met with complications. The practical limit appears to be drawn by the insolubility, tetrakisazobenzene and its diamino compound being, at present, the highest uniform and pure substance of this series.

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Valori, Atti Accad. Lincei 5 23, II, 212 (1914).

Reported by J. W. Shackleton
November 7, 1938

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THE REDUCTION OF ORGANIC COMPOUNDS ON THE DROPPING MERCURY CATHODE

Winkel and Proske -- Kaiser Wilhelm Institute

A large number of organic compounds have been investigated, and it is found that the potential at which a compound is reduced upon a dropping mercury cathode is a constant characteristic of the compound in question. This potential is called the "depolarization potential" and differs from the true reduction potential by the amount of the overvoltage on the mercury electrode.

The depolarization potential is measured by means of a polarograph in the following manner. The compound is dissolved in water (or in dilute alcohol if necessary) containing an auxiliary electrolyte such as ammonium chloride. This solution is made the electrolyte in a cell containing a layer of mercury as anode and a dropping mercury cathode. When a steadily increasing potential is applied across the cell, little change in the current passing through the cell is observed until a critical potential is reached, at which point there is a sudden, large increase in the current. This potential (E') is noted carefully, and the depolarization potential is calculated from the equation:

$$\text{Depolarization Potential} = E' - E_a - (IR).$$

E_a, the anode potential, is found by means of a calomel electrode. The IR drop across the cell is negligibly small in the presence of ammonium chloride or other strong electrolyte.

The depolarization potential is dependent upon many factors, including the pH of the solution, temperature, concentration of substance and auxiliary electrolyte, and the nature of the added electrolyte. The effects of all of these, with the exception of pH, are not important. The value of the increase in current varies with the concentration and diffusion rate of the substance, the pH of the solution, the sensitivity of the current measuring device, the nature of the capillary used in the dropping electrode, and the temperature. These factors are constant for a given set-up and need not be considered in most cases.

The method is highly sensitive. The concentration of the organic compound is usually about 10^{-3} M while that of the auxiliary electrolyte is 0.1 N. Recent refinements in technique, however, permit accurate measurement of the depolarization potential using 0.01 ml. solution containing 10^{-9} g. of substance.

The following classes of organic compounds have been studied: carbonyl compounds (including sugars), azo compounds, nitro compounds, and unsaturated compounds such as ethylenes and acetylenes. The carbonyl compounds have been studied in greatest detail. The ease of reduction of carbonyl compounds has been found to depend on the structure. Dialkyl ketones are not reduced unless they contain halogen or hydroxyl substituents.

Aliphatic aldehydes are readily reduced, but the potential becomes constant after and including acetaldehyde. Aromatic aldehydes and ketones and aryl alkyl ketones are all easily reduced. Saturated monobasic and dibasic acids, with the exception of oxalic acid, are not reducible; however, acids containing a carbonyl group in addition to the carboxyl group are reduced. In aromatic compounds, the position of substituents on the ring affects markedly the depolarization potential. This is shown by the following table of depolarization potentials for benzaldehyde and certain of its derivatives.

Benzaldehyde	1.27 volts
o-Chlorobenzaldehyde	1.07
m-Chlorobenzaldehyde	1.12
p-Chlorobenzaldehyde	1.18
o-Hydroxybenzaldehyde	1.28
m-Hydroxybenzaldehyde	1.21
p-Hydroxybenzaldehyde	1.36

Various groups may be classified according to their effect upon the depolarization potential as follows:

I. Those increasing the potential: CH_3-, -OH, -NH_2.
II. Those decreasing the potential by more than 0.2 volt: -CH_2I, -CH_2Br, -CH_2Cl, -$C_{10}H_7$, -C_6H_5, -$COCH_3$, -COOH, -C_6H_4Cl(o).
III. Those decreasing the potential less than 0.2 volt: -C_6H_4Cl(m), -C_6H_4Cl(p), -C_6H_4Br(m), -C_6H_4Br(p), -CH_2OH, -CH_2COCH_3.

The effect of a single group upon different molecules cannot be quantitatively determined in all cases as yet because it depends upon the absolute value of the reduction potential. However, for depolarization potentials of from 1.0 to 1.5 volts, the effect of the methyl group is constant and equal to +0.20 volts.

These polarographic data have been shown to be closely correlated with ultraviolet absorption and with Raman spectral data. Thus, for compounds in the same homologous series, the depolarization potential decreases as the wave length of the first ultraviolet absorption maximum increases. A decrease in the frequency of vibration of the carbonyl group, as disclosed by Raman spectra, is accompanied by increased ease of reduction.

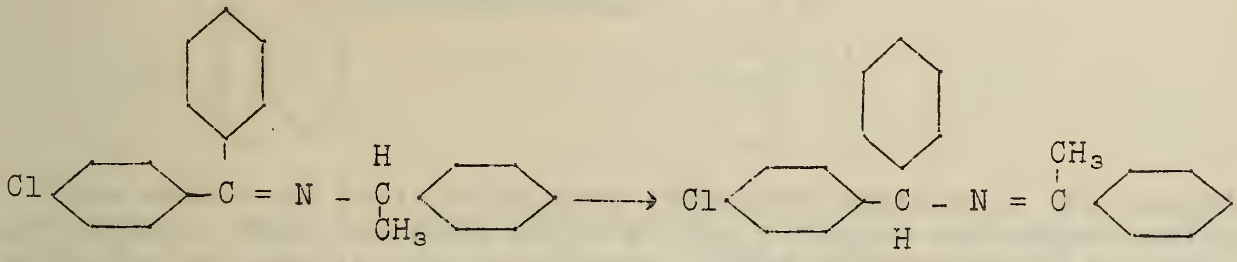
The effect of a conjugated system is particularly striking. Quinone and quinhydrone are reduced at almost immeasurably low potentials. Acetophenone is easily reduced, but benzyl methyl ketone cannot be reduced.

APPLICATIONS

Depolarization potentials furnish a very convenient method for qualitative organic analysis, especially where the amount of material is too minute to permit isolation and identification by the usual methods. Further investigation is expected to disclose the reasons

for the remarkable effect of substituents upon the depolarization potential and for the correlation with ultraviolet absorption and Raman spectral data. The depolarization potential will then become very useful in the determination or confirmation of structure of molecules.

Determination of the amount of current increase at the depolarization potential leads to a quantitative measurement of the amount of substance present. This applies to a solution of a single carbonyl compound or to a mixture. In the latter case, both the relative ratios and the absolute quantity present can be determined in one operation. The accuracy of such quantitative determinations is of the order of 2 per cent, and, as has been mentioned, the amount of any compound present need not exceed 10^{-9} g. Adkins and co-workers have applied the polarographic analytical method to the study of the tautomerization of 1-p-chlorobenzhydrylidene α-phenylethyl amine (I) to α-phenylethylidene p-chlorobenzhydrylamine.



I.

Polarographic methods have also been applied to the investigation of soap solutions, the study of albumins, the electroreduction of acataldehyde, researches on wines, microanalysis of reducible substances in fermentation products, decomposition of saccharose, analysis of petroleum and distillates for reducible substances and adsorbable matter, and to the effects of fatty acids and dyes upon certain inorganic processes.

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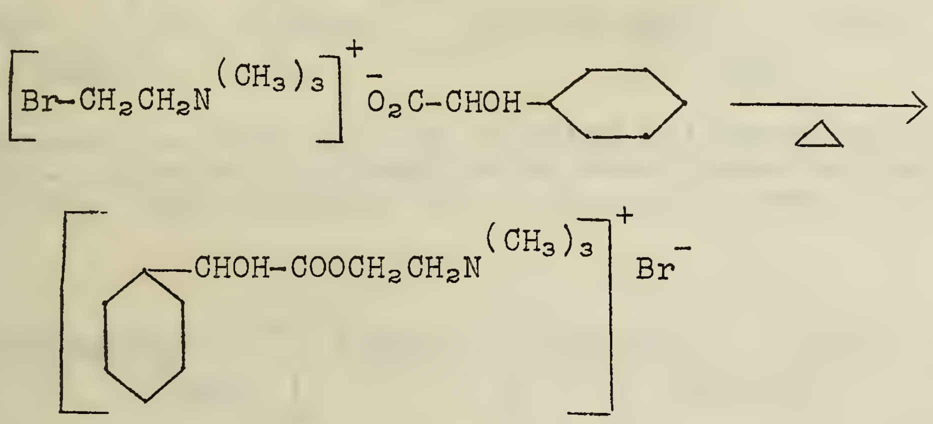
Reported by H. M. Teeter
November 16, 1938

A NEW REARRANGEMENT AND ITS USE IN THE PREPARATION OF ESTERS OF AMINO ALCOHOLS

Horenstein and Pählicke -- The Chemical Works of
Dr. Joachim Wiernik and Company, Inc., Berlin.

Horenstein and Pählicke observed that when the mandelic acid salt of bromocholine was heated a rearrangement took place which produced the bromide of choline mandelate.

(1)



The amount of ionized bromide increased rapidly as the reaction proceeded. Thus the acid anion on the nitrogen exchanged position with the halogen in the side chain. This rearrangement occurred with all salts investigated (over 30).

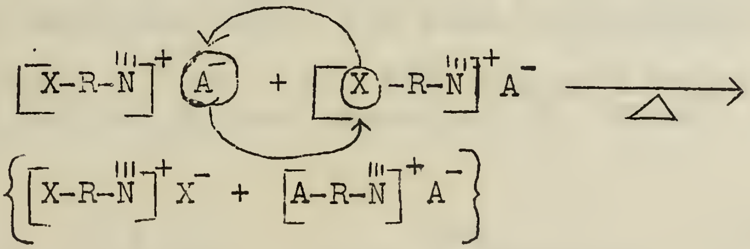
According to the authors nothing like it was found in the literature.

This rearrangement took place with both organic and inorganic acids. In some cases the tendency for rearrangement was so great that it was necessary to isolate the salt before heating.

An attempted explanation of the rearrangement is as follows:

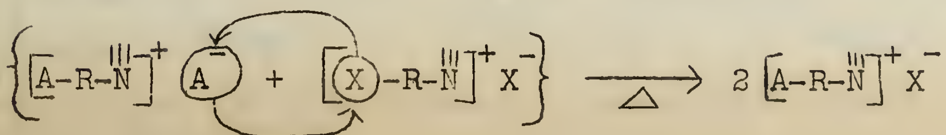
R = alkyl group
X = halogen replaced by A
A = acid anion which forms ester

(a)



$$[X-R-\overset{|||}{N}]^+ A^- + [X-R-\overset{|||}{N}]^+ A^- \xrightarrow[\Delta]{} \{[X-R-\overset{|||}{N}]^+ X^- + [A-R-\overset{|||}{N}]^+ A^-\}$$

(b)



$$\{[A-R-\overset{|||}{N}]^+ A^- + [X-R-\overset{|||}{N}]^+ X^-\} \xrightarrow[\Delta]{} 2\,[A-R-\overset{|||}{N}]^+ X^-$$

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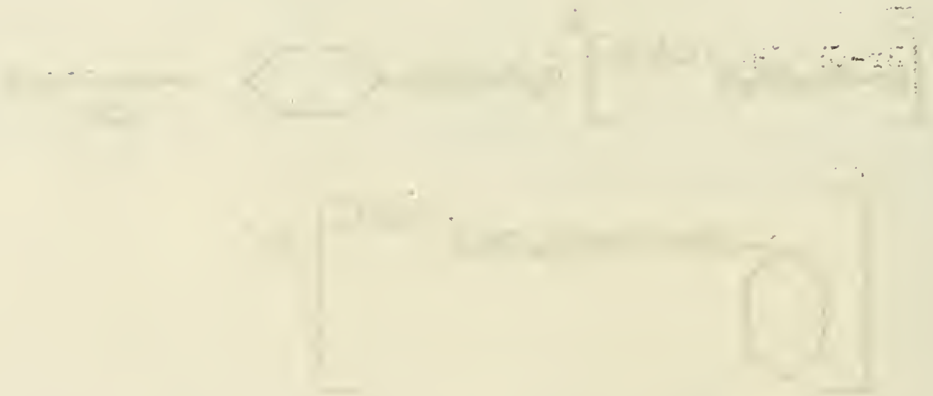

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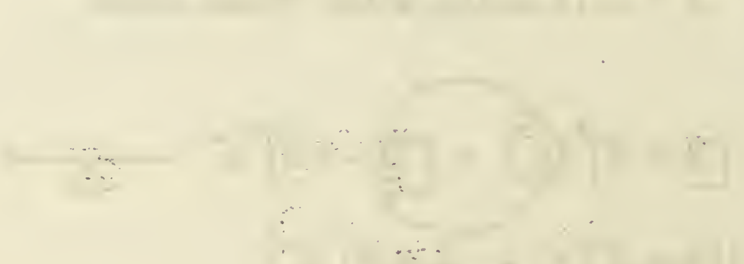
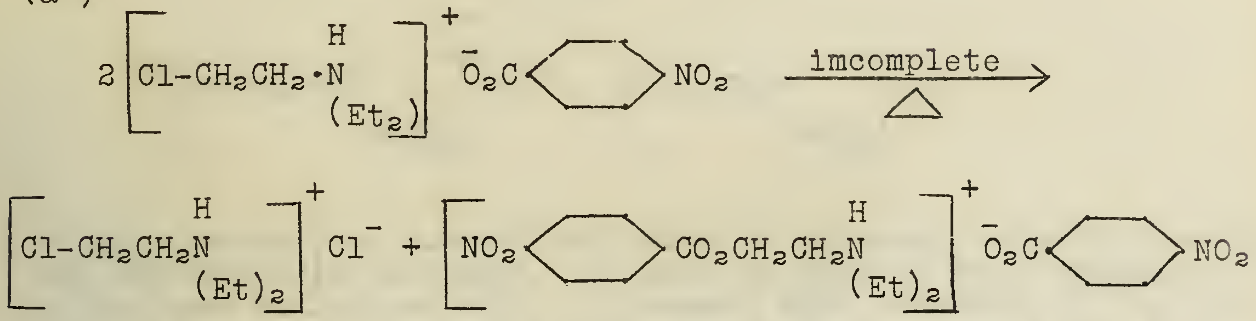


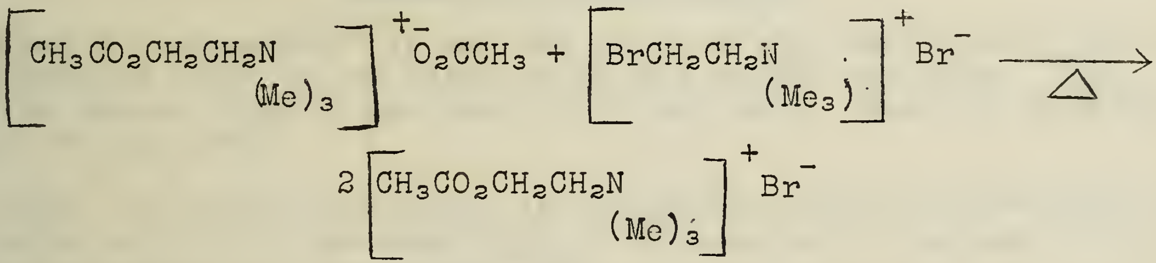
If this is correct, the compounds on right side of equation (a) should be detected in the reaction mixture if rearrangement is stopped before it is completed.

(a')



Both compounds on right side of equation (a') were isolated and identified. Equation (b) should also take place independently of equation (a). This actually takes place as in equation (b').

(b')



$$\left[CH_3CO_2CH_2CH_2N(Me)_3\right]^{+}\bar{O}_2CCH_3 + \left[BrCH_2CH_2N(Me_3)\right]^{+}Br^{-} \xrightarrow[\Delta]{} 2\left[CH_3CO_2CH_2CH_2N(Me)_3\right]^{+}Br^{-}$$

This explanation of the rearrangement in equations (a) and (b) is not positive as yet although there are no contradictions. In all rearrangements given, X in equation (a) was a halogen. This rearrangement was reported on salts of only tertiary amines and quaternary ammonium salts. More research is to be done to determine just what acid anions other than the halogens in the position of X in equation (a) will permit the rearrangement to take place.

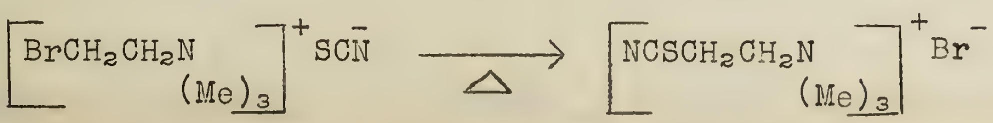
This method of esterification is very mild since the rearrangement takes place in a neutral medium.

Esters of Inorganic Acids

Since the esters of amino alcohols and inorganic acids are not important in medicine only a few were investigated.

In the series $\overline{I}$, $\overline{Br}$, $\overline{Cl}$, $\overline{SCN}$ the acid anion on the nitrogen is replaced only by the one preceding it. Thus:

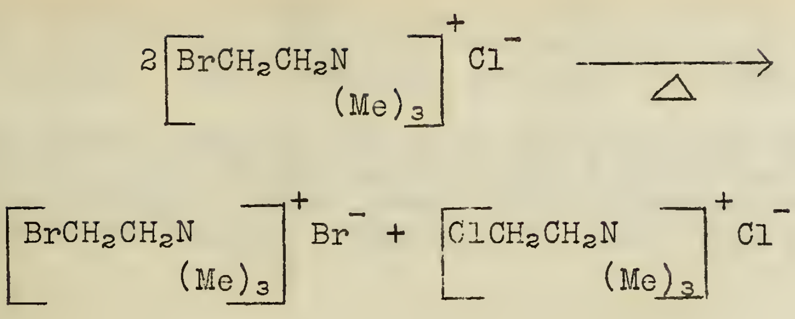
(2)



$$\left[BrCH_2CH_2N(Me)_3\right]^{+}\overline{SCN} \xrightarrow[\Delta]{} \left[NCSCH_2CH_2N(Me)_3\right]^{+}Br^{-}$$

Bromocholine chloride produced bromocholine bromide and chlorocholine chloride (3).

(3)



$$2\left[\mathrm{BrCH_2CH_2N(Me)_3}\right]^+\mathrm{Cl}^- \xrightarrow{\Delta} \left[\mathrm{BrCH_2CH_2N(Me)_3}\right]^+\mathrm{Br}^- + \left[\mathrm{ClCH_2CH_2N(Me)_3}\right]^+\mathrm{Cl}^-$$

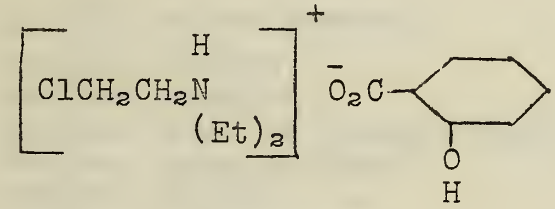
In the same manner iodocholine chloride produced iodocholine iodide and chlorocholine chloride. It will be noticed that reaction (3) is the same as (a) or (a'). It seemed that reaction (b) or (b') was not complete. In all rearrangements where both A and X in equation (a) were halogens there was produced a mixture of halides which was very hard to separate.

Esters of Organic Acids

When A in equation (a) was the anion of an organic acid the rearrangement produced an ester which was easily purified. The yields varied from 50 per cent to 83 per cent. Most of them were about 75 per cent.

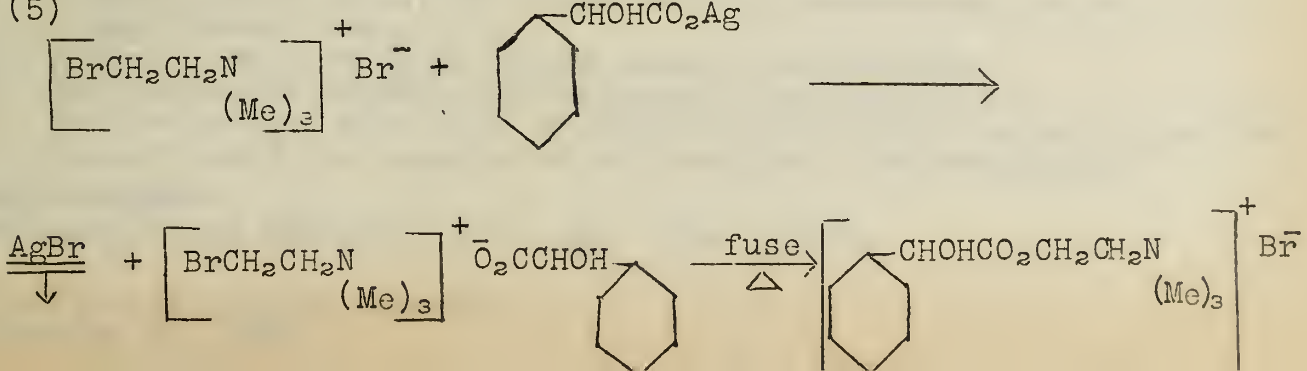
There are three variations in the method for esterification all of which arrive at the same type of intermediate compound before the rearrangement takes place (4).

(4)



I. The halide salt of the amino alcohol with OH group replaced by a halogen is dissolved in water and a water solution of the silver salt of the desired acid is added. The silver halide is filtered off and solution is evaporated to dryness in a vacuum. The residue is fused on oil bath. Compounds 1-7 were made in this manner.

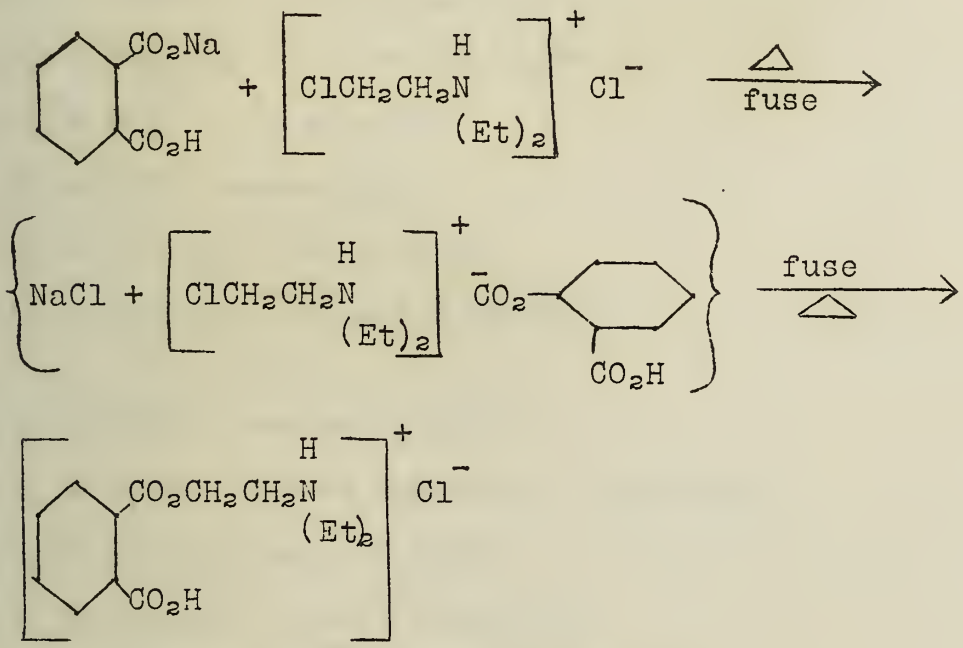
(5)



II. The free basic amino alcohol with OH group replaced by a halogen is neutralized with the desired acid in a suitable solvent and is refluxed. This procedure was used on compounds 8-13, 17.

III. The sodium salt of the acid is fused with the halide salt or hydrohalide salt of the amino alcohol which has the OH group replaced by a halogen. This method also allows a partial esterification of polybasic acids. Compounds 7, 13-16 were made by this method.

(6)



Compounds made by this rearrangement:

1. Bromide of choline lactate.
2. Bromide of choline pyruvate.
3. Bromide of choline ester of phenylquinolinecarboxylic acid.
4. Bromide of choline desoxycholate.
5. Bromide of choline cholate.
6. Bromide of choline thiocyanate.
7. Bromide of choline mandelate.
8. Hydrochloride of β-diethylaminoethyl thiocyanate.
9. Hydrochloride of β-piperidinoethyl benzoate.
10. Hydrochloride of β-diethylaminoethyl salicylate.
11. Hydrochloride of 3-diethylaminopropyl cinnamate.
12. Hydrochloride of β-diethylaminoethyl mandelate.
13. Hydrochloride of β-diethylaminoethyl benzilate.
14. Hydrochloride of 2,2-dimethyl-3-diethylaminopropyl ester of *d,l*-tropic acid.
15. Hydrochloride of β-diethylaminoethyl monoadipate.
16. Hydrochloride of β-diethylaminoethyl monophthalate.
17. p-Nitrobenzoic acid salt of β-diethylaminoethyl ester of p-nitrobenzoic acid (an example of an incomplete rearrangement).

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Reported by Hugh W. Stewart
November 16, 1938.

THE FRIEDEL-CRAFTS REACTION

The Friedel-Crafts reaction finds extensive application not only in academic research but also in industry. The purpose of this paper is to point out the usefulness that the reaction has attained in organic chemistry. The following equations list the more important Friedel-Crafts reactions.

$$C_6H_6 + RCl \longrightarrow C_6H_5R$$

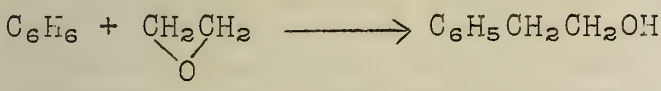
$$3C_6H_6 + CHCl_3 \longrightarrow (C_6H_5)_3CH$$

$$C_6H_6 + CH_2{=}CH_2 \longrightarrow C_6H_5CH_2CH_3$$

$$C_6H_6 + ROH \longrightarrow C_6H_5R$$

$$C_6H_6 + ROR \longrightarrow C_6H_5R$$

$$C_6H_6 + R'CO_2R \longrightarrow C_6H_5R$$



$$C_6H_6 + \underset{O}{CH_2CH_2} \longrightarrow C_6H_5CH_2CH_2OH$$

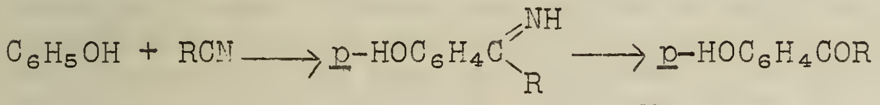
$$C_6H_6 + RCOCl \longrightarrow C_6H_5COR$$

$$C_6H_6 + COCl_2 \longrightarrow C_6H_5COCl + C_6H_5COC_6H_5$$

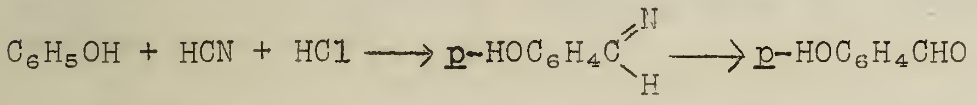
$$C_6H_6 + (RCO)_2O \longrightarrow C_6H_5COR$$

$$C_6H_6 + CH_2{=}C{=}O \longrightarrow C_6H_5COCH_3$$

$$C_6H_6 + RCOOH \longrightarrow C_6H_5COR$$



$$C_6H_5OH + RCN \longrightarrow \underline{p}\text{-}HOC_6H_4C\genfrac{}{}{0pt}{}{{=}NH}{-R} \longrightarrow \underline{p}\text{-}HOC_6H_4COR$$ (Hoesch-Houben Reaction)



$$C_6H_5OH + HCN + HCl \longrightarrow \underline{p}\text{-}HOC_6H_4C\genfrac{}{}{0pt}{}{{=}N}{-H} \longrightarrow \underline{p}\text{-}HOC_6H_4CHO$$ (Gattermann Reaction)

$$C_6H_5OH + CO + HCl \longrightarrow \underline{p}\text{-}HOC_6H_4CHO$$ (Gattermann-Koch Reaction)

$$C_6H_6 + ClCONH_2 \longrightarrow C_6H_5CONH_2$$

$$C_6H_6 + CO_2 \longrightarrow C_6H_5COOH$$

$$C_6H_6 + C_2H_5ONO_2 \longrightarrow C_6H_5NO_2$$

$$C_6H_6 + N_2O_4 \longrightarrow C_6H_5NO_2$$

$$C_6H_6 + C_6H_5SO_2Cl \longrightarrow C_6H_5SO_2C_6H_5$$

$$C_6H_6 + CSCl_2 \longrightarrow C_6H_5CSC_6H_5$$

Alkylation of Aromatic Compounds.--Friedel-Crafts alkylations differ from acylations in three important respects: (1) They need only a comparatively small amount of aluminum chloride, because the latter does not form a stable complex with the product of reaction, (2) they are readily reversible, (3) they are frequently accompanied by rearrangements in the carbon skeleton.

The variety of alkylating agents that have been employed in this synthesis is wide; among them are alkyl halides, aralkyl halides, olefins, alcohols, ethers, esters, and aldehydes. Calloway arrives at the conclusion that alkyl halides are the most reactive alkylating agents. The reversibility of alkylation is well known, and can be demonstrated in numerous ways; for example, in the interconversion between mono- and polyalkylbenzenes in the presence of aluminum chloride, and in the exchange of substituent groups studied by Fuson and coworkers. Generally neither the configuration of the entering group nor the orientation in the nucleus can be accurately predicted in alkylation.

Alkylation with methyl and ethyl chlorides is difficult to control, and all of the possible alkylated compounds are generally formed. The higher halides react to yield branched alkyl substances. The alkyl polyhalides also react as predicted to yield progressively phenylated compounds.

Good yields of ethylbenzene may be obtained by passing a stream of ethylene into rapidly stirred suspension of finely pulverized aluminum chloride in benzene. The higher members of the olefin series behave in a similar manner with the benzene ring adding to the carbon atom holding the least number of hydrogen atoms.

Alkylation with esters and ethers may find considerable application in the alkylation of highly sensitive molecules, since the complex formed between the ether or ester and condensing agent materially lessens the drastic resinifying and polymerizing action of the condensing agents. Syntheses in the thiophene series by means of ethers have been realized where all efforts with alkyl halides have failed.

Acylation of Aromatic Compounds.--Acid halides yield the expected ketones with no rearrangement of the acyl structure taking place. This ketone synthesis seems to be generally applicable to unsaturated acid halides, although some halides unavoidably give complicating reactions on account of the unsaturation. When oxalyl chloride is used in the synthesis of ketones, the nature of the product depends in a large measure on the substance undergoing substitution. Compounds that acylate with relative ease, such as anisole or dimethylaniline, yield diketones, while substances that acylate with more difficulty, such as benzene yield simple ketones as result of the decomposition of the oxalyl chloride by the condensing agent.

Generally anhydrides react with an aromatic nucleus to yield one equivalent of ketone for each mole of anhydride when two

equivalents of aluminum halide are used. It has recently been demonstrated that the remaining fragment from the anhydride may in part also acylate the ring to increase the yield. Phthalic anhydride may condense in another manner, since simultaneously with o-aroylbenzoic acid formation, there may be phthalide formation. The presence of foreign substances such as acetic anhydride, or non-equivalent quantities of the reactants favor the formation of phthalides.

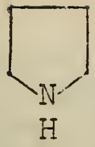
The aliphatic acids, such as acetic or propionic, when heated with an excess of aluminum chloride in benzene give ketones in good yields. Three moles of aluminum halide are required for each mole of ketone formed.

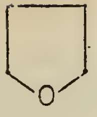
Urea chloride readily introduces an amide group into the more active structures as naphthalene, phenol ethers, and alkylbenzenes. The reaction between phosgene and aromatic hydrocarbons can proceed to yield mono-substitution products by adopting a short reaction period and using an excess of the phosgene.

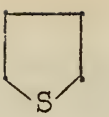
Friedel-Crafts Substitutions in Heterocyclic Compounds.--The heterocyclic compounds are highly sensitive to drastic condensing agents, or they form complexes with the metal so that substitution in the Friedel-Crafts reaction is inhibited. Attempts to acylate unsubstituted heterocyclic rings, such as pyrrole, thiophene, or furan, have been fairly successful, but efforts to alkylate these rings have been generally unsuccessful. Methyl furoate will acylate in the 5-position by means of an acid chloride or an anhydride to yield a ketone, but efforts to acylate nitrofuran have been futile. Thiophene has been acylated in excellent yields. Apparently the only unsubstituted nitrogen ring which has been acylated by the Friedel-Crafts method is pyrrole, and the latter will acylate without a catalyst when it is refluxed with acetic anhydride.

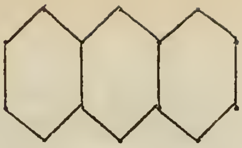
Friedel-Crafts Substitutions in Aliphatic Compounds.--Friedel-Crafts syntheses are most commonly concerned with aromatic nuclei, but reactions with aliphatic compounds are well known. For example, efforts to bring about ortho-intra-ring closures of 5-phenyl-n-amyl chloride did not yield the desired substance, but gave instead cyclopentylbenzene in eighty-four per cent yields. Other examples are the preparation of cyclohexenyl methyl ketone from acetyl chloride and cyclohexene, and the synthesis of phenylvinyl ketone from ethylene and benzoyl chloride in the presence of aluminum chloride.

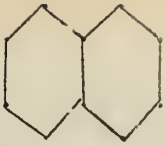
Activating and Inhibiting Groups.--With the exception of pyridine, unsubstituted rings will generally undergo the Friedel-Crafts substitutions. These rings perhaps may be arranged in the following series which represents an order of their decreasing ease of substitution.

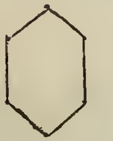


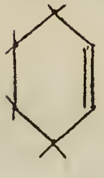


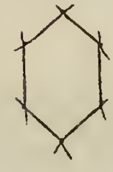


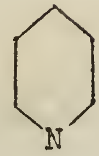












This series is not exact for all alkylations and acylations, but it possesses considerable merit from a qualitative standpoint.

Substituents in a ring modify the relative ease with which Friedel-Crafts substitutions may take place, and the effect may be either positive or negative in character. Judging from numerous comparisons Calloway suggests that the following series represents the order of decreasing activation upon a ring.

-OH   Cl-   -CHO

$-OCH_3$, $(CH_3)_2N-$, CH_3-, H-, Br- , $-COCH_3$, -COOR, $-NO_2$, -CN

I-

In general, an increasing electronegativity of the group increases the difficulty of substitution. This series should not be accepted too rigorously, since it only offers a qualitative comparison. Methyl benzoate, benzonitrile, benzoic acid, and nitrobenzene will not undergo a Friedel-Crafts substitution in the presence of aluminum chloride. However, the character of the latter compounds is modified by the introduction of a group such as methoxyl which activates the nuclear hydrogens to such a degree that substitution may take place. Thus nitroanisole and methyl anisate can be acylated with ease. Alkyl groups activate ketones sufficiently to permit substitution, although the keto group itself so markedly inhibits the reaction that only mono-keto substances may be obtained when benzene is acylated. Thus two acetyl groups may enter mesitylene and durene.

Reliability.--Generally alkylations are more variable and unreliable than acylations, but it must be remembered that the reliability of the reaction depends on several factors. Among these contributing effects are the nature and purity of the catalyst, the solvent, the alkylating or acylating reagent, the substance undergoing reaction, the foreign bodies present, and temperature. Substituents already present in a nucleus generally direct normally as they would for other substitution reactions, such as nitration and halogenation, although this is not always true. Secondly, alkyl halides undergo rearrangement during reaction to give, usually, the most highly branched alkyl groups. Besides the rearrangement, the alkyl group may be cleaved to yield short alkyl groups; that is, a long chain alkyl halide, for instance amyl or

hexyl, may yield on reaction a butyl group. Under the influence of aluminum chloride, even the halogens attached to the aromatic nuclei may migrate in the ring or to another ring. Generally, high temperatures, high concentration of condensing agent, and a long reaction time favor the side reactions, although these same conditions may be required to effect the condensation.

Solvents and Catalysts.--Frequently in acylations the solvent is an excess of the reacting aromatic hydrocarbon. Among the inert solvents carbon disulfide, petroleum ether, and nitrobenzene find considerable favor. Carbon disulfide appears to have the specific action inhibiting the migration of groups. When highly reactive compounds or mild condensing agents are employed, solvents that would react under normal conditions may be used. Thus, benzene can be employed as a solvent for the acylation of furan, and anthracene can be acylated in benzene solution by phthalic anhydride and aluminum chloride. Nitrobenzene finds its use as a solvent not only as a result of its high boiling point and excellent solvent nature, but largely because of its ability to moderate, sometimes to a remarkable degree, the course of certain reactions. The moderating influence may be attributed to the fact that nitrobenzene forms a loose aluminum chloride complex which lessens the activity of the aluminum chloride, like phenols, amines, and benzyl halides. The solvent may also possess a catalytic effect, since in the preparation of benzaldehyde from carbon monoxide and benzene, the use of nitrobenzene as a solvent makes possible carrying out the reaction at normal instead of 1,000 pounds pressure.

Strictly speaking, the Friedel-Crafts reaction entails the use of aluminum chloride. However, other metallic halides such as boron trifluoride, stannic chloride, ferric chloride, and zinc chloride effect similar condensations. Of these, boron trifluoride has found the widest application.

The Mechanism of the Friedel-Crafts Reaction.--It has not yet been found possible to establish a mechanism which will hold for all the syntheses which come under the classification of a Friedel-Crafts reaction. Theories have been advanced, but not definitely confirmed, for each type reaction. In general, the suggested theories are:

1. Perrier and Boeseken: Formation of an addition complex between the acid chloride and the aluminum chloride. This complex reacts with the aromatic hydrocarbon with the elimination of hydrogen chloride. Hydrolysis then yields the free ketone.

2. Meerwein: The addition complex is a salt of the type $(RCO^+)(AlCl_4^-)$.

3. Wieland: Addition of the acid chloride to the double bond followed by the elimination of hydrogen chloride.

4. Friedel and Crafts: Aluminum chloride forms an addition compound (R-Al_2Cl_5) with the aromatic hydrocarbon with the loss of hydrogen chloride.

5. Others: No intermediate compound formation; merely a physical weakening of the C-H and C-Cl linkages.

In testing these hypotheses, Wertyporoch and Wohl arrived at the following conclusions:

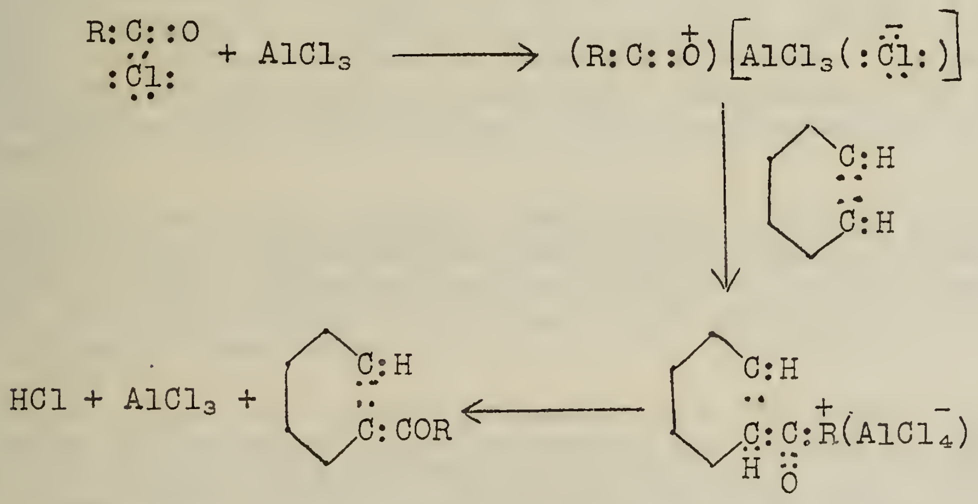
1. Meerwein's salt is formed first.

2. This salt adds the aromatic compound to yield a strongly conducting salt, $(C_6H_6,COCH_3^+)(AlCl_4^-)$.

3. The nuclear C-H bond is weakened in the complex cation and elimination of hydrogen chloride completes the reaction.

4. There is no evidence that the aluminum chloride reacts separately with the aromatic hydrocarbon under the conditions of the reaction.

This is the mechanism which is most widely accepted today. Placed on an electronic basis we have:



This may be applied equally well with alkyl halides. Alkylations with olefins or paraffins are said to go through the alkyl halide since a trace of hydrogen chloride (or moisture which will hydrolyze some of the aluminum chloride to give water) is believed to be necessary in every case.

It is interesting to note that alkylation is definitely a reversible reaction whereas acylation is believed not to be even though the removal and migration of acyl groups have been reported.

Industrial Utilization of the Friedel-Crafts Reaction.--The number and types of Friedel-Crafts syntheses have been increased to such an extent in recent years that the reaction has now become

the basis for the industrial preparation of many new and useful compounds. The dye, detergent, pharmaceutical, lubricating oil, resin, perfume, and antiseptic industries represent only a few of those that have now recognized the value of this general method of synthesis.

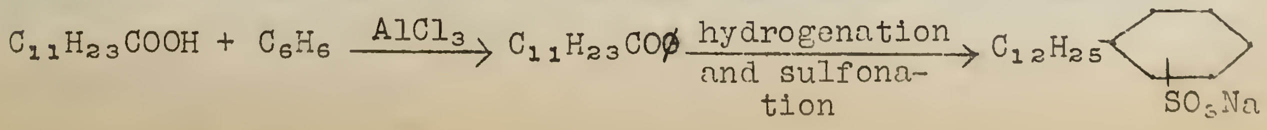
One of the simpler examples is the addition of 30° of isopropyl chloride to m-cresol to yield thymol which finds use as an antiseptic. Of a slightly different type is the addition of phenol to oleyl alcohol to give oxyphenyloctadecyl alcohol, a compound which is a valuable antiseptic and germicide and also may be condensed with formaldehyde to give a resin or converted to the sulfonic acid to yield a compound which is an excellent wetting agent.

More recent applications are in the synthesis and purification of lubricating oils, the preparation of Paraflow, and the cracking of hydrocarbons for the purpose of preparing valuable oils. Fischer in Germany has worked out three different methods for the preparation of lubricating oils. The first process starts with the higher boiling fraction from the Fischer-Tropsch benzine synthesis. Chlorination of this fraction followed by treatment with aromatic hydrocarbons in the presence of aluminum chloride gives lubricating oils of any desired viscosity. The second process treats Kogasins containing 1,2-chlorine atoms with activated aluminum. This gives lubricating oils comparable to the standard Pennsylvania stock. The third process is of particular note since in this case the monoolefins contained in Kogasin I are subjected, without prior chlorination, to polymerization by aluminum chloride. In general, the products may be attributed to cracking, alkylation, and polymerization reactions which may proceed either independently or simultaneously.

In addition, from certain fractions of cracked petroleum may be obtained, by polymerization under the influence of aluminum chloride, a large number of resins which have found a variety of uses in industry. Other resins have been synthesized directly from simple organic compounds.

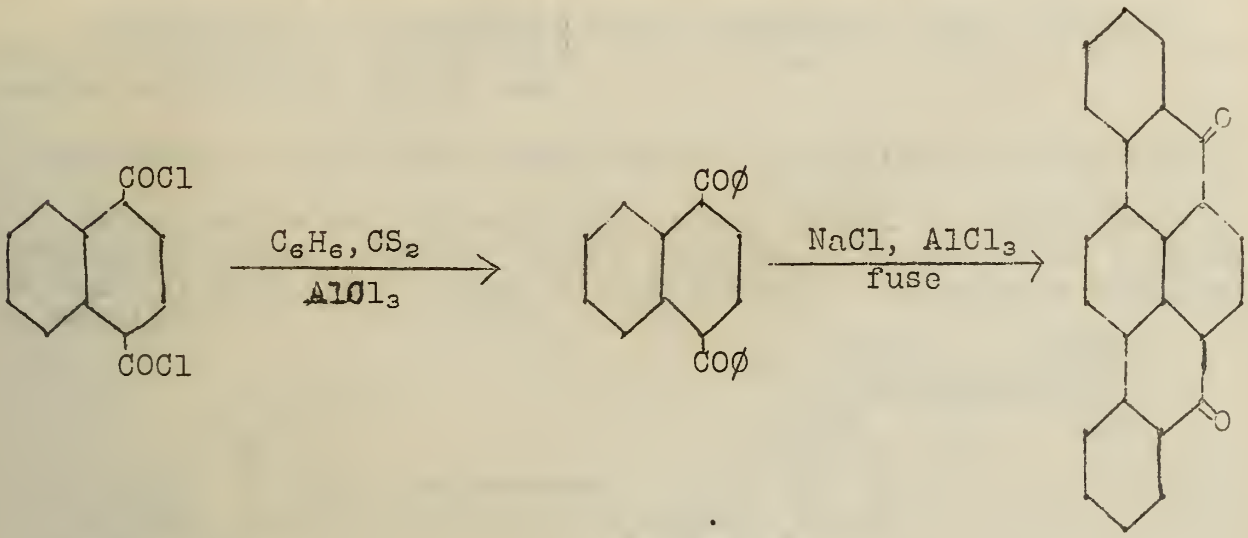
In the field of textile preservatives the action of certain phenols on chlorinated benzyl chlorides has become of importance. The condensation products obtained by the action of triphenyl-, tritolyl-, trinaphthyl-, and tribiphenylmethyl chlorides on compounds such as diphenylamine, phenyltolylamine, and phenylnaphthylamine are now important as aging preventives for rubber.

The rather recent development of ketone synthesis by the condensation of the comparatively cheap aliphatic acids with aromatic hydrocarbons has led to the commercial preparation of compounds which are excellent washing, wetting, and emulsifying agents. Thus:



$$C_{11}H_{23}COOH + C_6H_6 \xrightarrow{AlCl_3} C_{11}H_{23}CO\phi \xrightarrow[\text{and sulfonation}]{\text{hydrogenation}} C_{12}H_{25}\text{—}C_6H_4\text{—}SO_3Na$$

In addition to the well known anthraquinone dyes, many compounds important to the dye industry are now produced commercially with the aid of aluminum chloride. An interesting example is the synthesis of 4,5,8,9-dibenzpyrene-3,10-quinone:



An isomer of this compound is prepared by the condensation of benzanthrone and benzoyl chloride followed by ring closure under the influence of aluminum chloride.

For certain carcinogenic hydrocarbons have been found comparatively simple methods of synthesis. Thus, 1,2-benzanthracene and 3,4-benzpyrene are now easily available.

Other examples include the syntheses of various P-, O-, S-, Se-, and As-containing hydrocarbons, the addition reactions of cyanoacetyl chloride and of malononitrile to give important dye intermediates, the syntheses of certain sulfanilamide derivatives, rearrangements catalyzed by aluminum chloride, and an innumerable number of analogous reactions, a large number of which find important commercial applications.

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Reported by Joseph Dec
and R. S. Long
November 23, 1938.

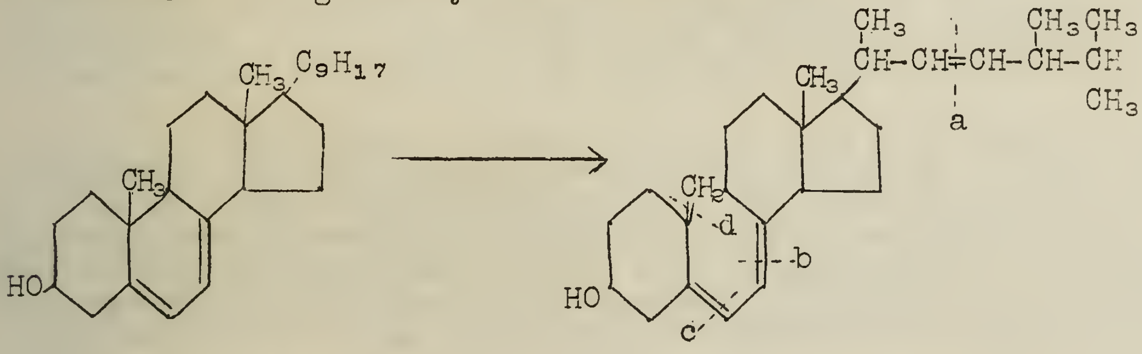
VITAMIN D_2

Windaus -- University of Göttingen
Dimroth -- University of Göttingen

Irradiation of ergosterol with ultraviolet light produces several compounds, one of which is calciferol or Vitamin D_2. The series of products formed are:

ergosterol ⟶ lumisterol ⟶ tachysterol ⟶ calciferol ⟶ toxisterol

Since calciferol is produced from a sterol it should have a structural formula similar to the sterols. The empirical formula is $C_{28}H_{44}O$ which is the same as ergosterol. The formula assigned to calciferol is given by II.



ergosterol (I) calciferol (II)

The following experimental facts have led to this structure:

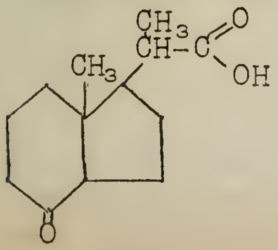
1. Lettré proved that it was tricyclic since it gave no phenanthrene derivatives on catalytic dehydrogenation with selenium.

2. Kuhn and Möller demonstrated presence of four double bonds by catalytic hydrogenation.

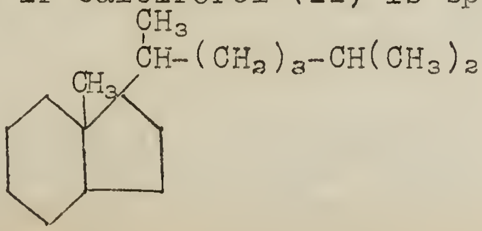
3. Ozonization of the maleic anhydride addition compound, or of calciferol itself, both give the keto acid, $C_{13}H_{20}O_3$, which can be formed by splitting calciferol (II) at a and at b thus giving the formula III for the acid.

4. Ozonization of calciferol, as well as ergosterol, lumisterol and tachysterol, yields methyl isopropyl acetaldehyde, which was isolated by Guiteras.

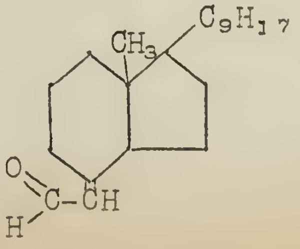
5. By ozonization of dihydrocalciferol, side chain saturated, Windaus obtained the ketone $C_{19}H_{34}O$ which can have the structural formula IV if calciferol (II) is split at b.



III



IV



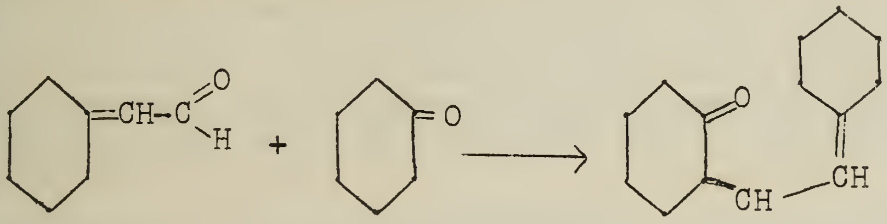
6. On addition of maleic anhydride two different addition products result which can be ozonized to yield ketone III.

7. Dehydrogenation of maleic anhydride addition product with selenium gave 2,3-dimethylnaphthalene, and with palladium gave β-naphthoic acid and naphthalene.

8. Oxidation of calciferol with $KMnO_4$ gave about a thirty per cent yield of HCOOH from the methylene group. However, Windaus obtained a few per cent of HCOOH from ergosterol, which contains no $=CH_2$ group, but Heilbron got practically no formic acid from ergosterol.

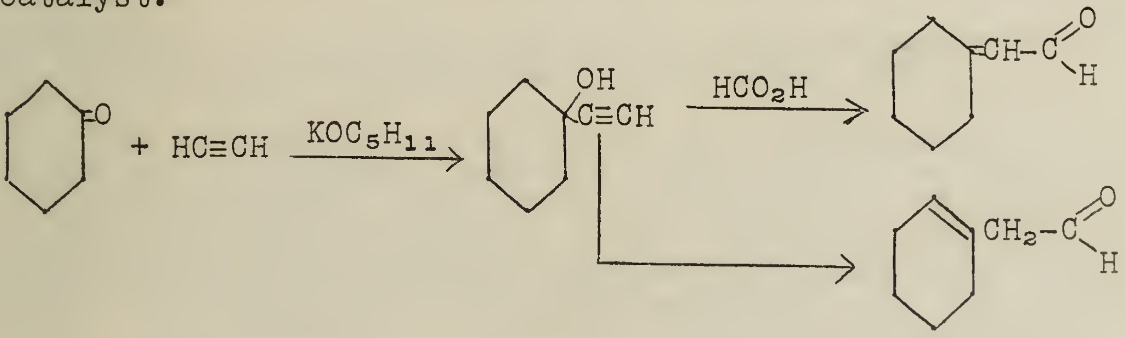
9. Careful oxidation of calciferol with CrO_3 in acetic acid yields an aldehyde, $C_{19}H_{34}O$, which gives an absorption spectra very similar to other α,β-unsaturated aldehydes. Therefore, it can be represented by formula V if calciferol (II) is split at c.

Since this evidence seems to point to formula II for calciferol, the next step is to try the synthesis of this compound or similar ones. Dimroth, working in the same laboratory as Windaus, has attempted to synthesize simple compounds which contain the conjugated semicyclic double bond system present in calciferol. The procedure he decided to follow was to condense cyclohexylidene acetaldehyde (VI) with cyclohexanone and then to replace =O by $=CH_2$.



VI VIII

The preparation of cyclohexylidene acetaldehyde (VI) and other α,β-unsaturated cyclic compounds has been described previously by Rupe. He prepared this aldehyde by condensing acetylene with cyclohexanone and rearranging the compound using formic acid as catalyst.

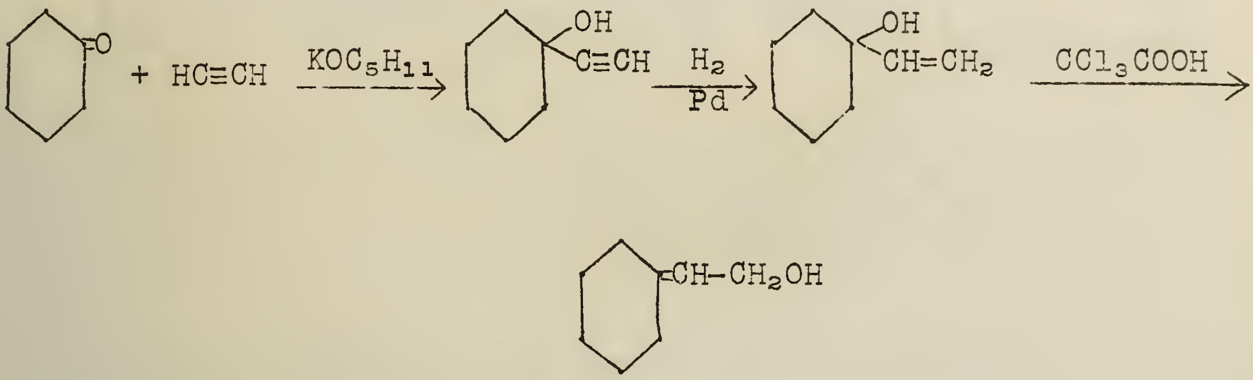


VI

IX

However, Hurd and Christ, and Fischer and Lowenberg independently have shown conclusively that instead of getting cyclohexylidene acetaldehyde (VI) its isomer acetyl cyclohexene (IX) was obtained by Rupe. Fischer and Lowenberg have tried other rearrangements and found that ethylene alcohols will rearrange to α,β-unsaturated alcohols using strong acid as a catalyst.

Dimroth decided to try this reaction on 1-ethylene cyclohexanol which he prepared by adding acetylene to cyclohexanone in the presence of potassium isoamylate. The product was then catalytically reduced to the ethylinic compound.

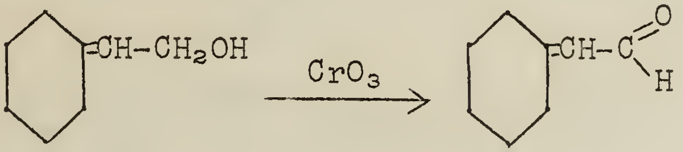


VIII

The addition product gives an 85 per-cent yield of 1-acetylene cyclohexanol which can be quantitatively reduced to the ethylene derivative.

The final step was then tried using acetic anhydride as a catalyst but the yield of cyclohexylidene ethyl alcohol (VIII) was poor. The best results were obtained using trichloracetic acid as a catalyst, from which yields of forty to fifty per cent were obtained. The yield was cut down due to splitting out of H_2O to form vinylcyclohexene.

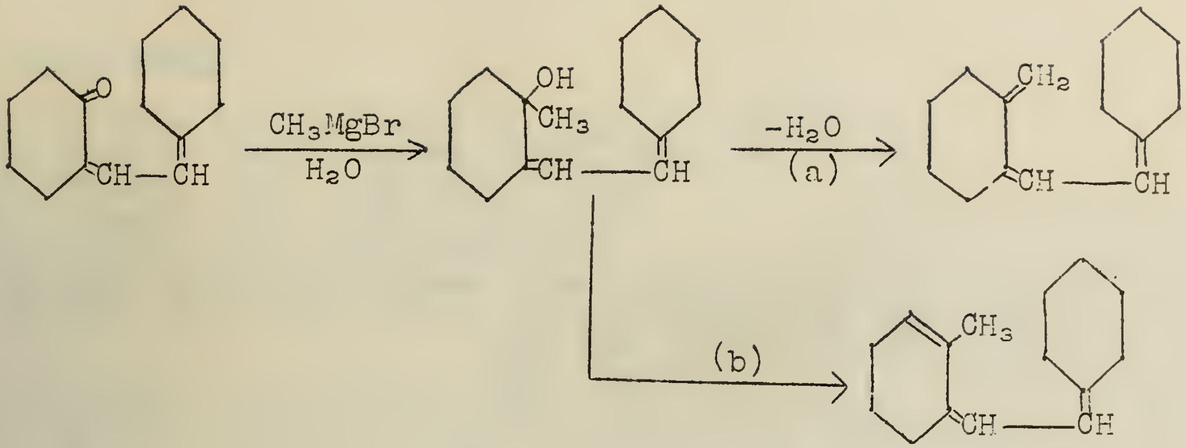
The alcohol was carefully oxidized to the aldehyde dropping CrO_3-CH_3COOH mixture into a benzene solution of the alcohol (VIII).



If carried out carefully, very little acid was produced and the yield of the aldehyde was forty to fifty per cent.

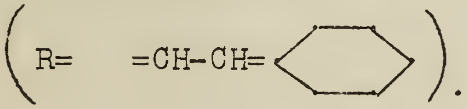
The condensation of aldehydes with cyclohexanone has been worked out by Vorländer and Kunze, who carried out their experiment using benzaldehyde. They found that the type of product obtained depended on the conditions of media and alkali strength. Based on these experiments, Dimroth condensed cyclohexylidene acetaldehyde (VI) and cyclohexanone in the presence of one per cent aqueous NaOH. The product was purified by extraction with ether and subsequent vacuum distillation. The product is very sensitive to air and, therefore, difficult to purify.

The replacement of the =O with a $=CH_2$ group presented difficulty since, with CH_3MgBr the tertiary alcohol is formed which can split out H_2O in two ways, the latter (b) being the easier.

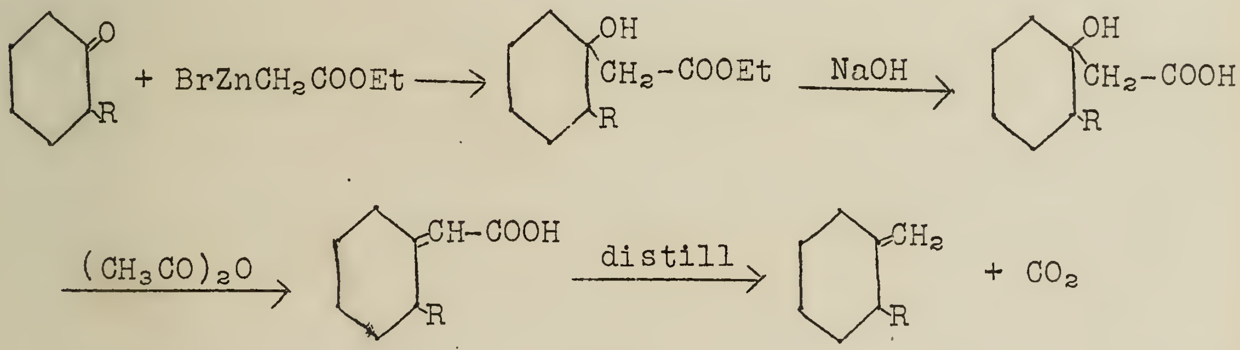

O
CH—CH
CH₃MgBr
H₂O
OH
CH₃
CH——CH
-H₂O
(a)
CH₂
CH——CH
(b)
CH₃
CH——CH

The compound produced by (b) should also be of interest as it may represent the ring system in tachysterol, but has not been studied as yet.

The Reformatsky reaction may be used to introduce $=CH_2$ in slightly better yields than alone but still not good



The product X is a heavy yellow oil which is very sensitive to air oxidation and hard to purify. The principal studies so far have


O
R
+ BrZnCH₂COOEt
OH
CH₂-COOEt
R
NaOH
OH
CH₂-COOH
R
(CH₃CO)₂O
CH-COOH
R
distill
CH₂
R
+ CO₂

been absorption spectra. It shows maximum absorption at 280 mμ, closer to tachysterol than calciferol.

Aldersley and Burkhardt have tried same reactions to produce same compound except in condensation they used four-acetyl cyclohexanone. The maximum absorption of their compound occurred 10 mμ toward the longer wave length than Dimroth's.

Further studies are being conducted to show whether substitutions on one or both rings will have as much effect on maximum absorption as 10 mμ.

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Reported by D. Burney
November 30, 1938

THE CHEMICAL SUBSTANCES RESPONSIBLE FOR THE COPULATION OF THE SEX CELLS OF THE CHLAMYDOMONAS EUGAMETOS IN LIGHT

R. Kuhn, F. Moewus, and D. Jerchel --
Kaiser Wilhelm Institute

It had been observed by Moewus that the sex cells of the Chlamydomonas Eugametos copulate in water solution in the presence of light, while, if the cells are kept in the dark no copulation occurs. Further experiments have shown the following fact to be true: If the active cells be removed from the illuminated solution and be replaced by cells which have not been exposed to light, copulation of the non-illuminated cells takes place even though the new solution is kept in the dark. From these data Kuhn postulated that under the influence of light a chemical substance (or substances) is formed and is given to the solution. This substance is of primary importance to the copulation of the sex cells. Since only light which is absorbed can act chemically, Kuhn concluded that he had to deal with a colored substance.

The Three Partial Photochemical Processes.--The changes which take place under the influence of light may be summarized: (1) Short period of illumination causes motion of the flagellae, the hair-like tails attached to the cells; (2) longer exposure renders the female sex cells capable of copulation; (3) still longer illumination activates the male cells to copulation.

The Effective Spectral Regions.--Experiments with monochromatic light have shown the following:

Source of Light	Wave Length	Motion of Flagellae	Copulation
Cd	643 mμ	+	-
Na	589	+	-
Hg	546	+	-
Hg	496	+	+
Hg	436	+	+

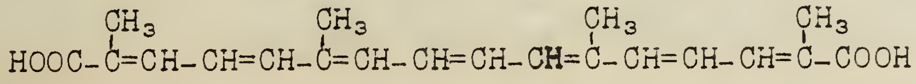
Motion of the flagellae occurs in red, yellow, green, blue and violet light. Copulation takes place only in the blue and violet regions.

The Effect of Oxygen.--In a sugar solution such as dextrose, lactose, raffinose or gentiobiose the cells showed motion of the flagellae even in the dark as long as oxygen was admitted. However, the "natural" motion-producing substance is just as effective when oxygen is excluded. In this way it is fundamentally different from the above-mentioned sugars.

Comparison of the Motion-producing Substance with Crocin.--

Concentration of an illuminated solution of the sex cells gives a small amount of orange-yellow substance. Hydrolysis of this sub-

stance and extraction with chloroform gives a golden yellow chloroform solution which shows absorption bands at 467 and 438 mμ. These bands agree very well with those of *trans*-crocetin.



$$\mathrm{HOOC-\overset{CH_3}{C}=CH-CH=CH-\overset{CH_3}{C}=CH-CH=CH-CH=\overset{CH_3}{C}-CH=CH-CH=\overset{CH_3}{C}-COOH}$$

Crocetin.--Similar hydrolysis and extraction of crocin from saffron gives absorption bands at 465 and 438 mμ. This indicates that hydrolysis of both the "natural" motion-producing substance and crocin yields *trans*-crocetin.

If crocin in CH_3OH is treated with alkali the dimethyl ester of *trans*-crocetin is obtained. Similar treatment of the orange-yellow substance mentioned above also yielded the dimethyl ester of *trans*-crocetin.

Colorimetric comparison with a standard crocin solution indicated that the active sex cell solution, after concentration contained 0.0205 mg. of crocin per cubic centimeter. Quantitative determinations of the amount of dextrose formed by the complete hydrolysis of the motion-producing substance showed 0.134 mg. Calculated on the assumption that the motion-producing substance is crocin, the value is 0.142 mg. of dextrose.

Further evidence that the motion-producing substance is crocin is the fact that crocin obtained from saffron also causes motion of the flagellae of the sex cells.

The points outlined above indicate rather conclusively that the motion-producing substance is crocin.

The Absolute Effectiveness of Crocin.--By repeated dilution of a solution of pure crocin and by observation of its effect on the sex cells, it was found that crocin is still effective in a dilution as great as one part in 250 trillion. Its power may be better realized by comparing it with the limiting dilution of other agents:

Adrenalin	---	1:20,000,000.
Biotin	---	1:400,000,000,000.
Crocin	---	1:250,000,000,000,000.

By counting the number of sex cells per cc. and by calculating the number of molecules of crocin present in one cc., it was found that each cell required one molecule of crocin.

Copulation Substances $K_♀$ and $K_♂$ as a Mixture of a Fore-stage V and a Final-Stage K_0.--Kuhn found that the substances required for copulation of the female and male cells, designated as $K_♀$ and $K_♂$, were mixtures of two substances which he called a "fore-stage" V and a "final-stage" K_0. Attempts to concentrate the "fore-stage" V from the active sex cell solution were unsuccessful. The "final-stage" K_0 is successively concentrated, how-

ever. A chloroform solution of the substance K_o showed absorption bands which agreed very well with those of the dimethyl ester of trans-crocetin. It was found that trans-crocetin dimethyl ester obtained from saffron was able to replace the natural "final-stage" K_o.

Since cis-crocetin dimethyl ester is known to rearrange in blue and violet light into the trans form, Kuhn assumed that the "fore-stage" V, which he could not concentrate, was the cis-isomer. This was confirmed by observing that the cis form obtained from saffron possessed the same power of activating the sex cells as the "fore-stage" V.

Specificity.--The foregoing experiments permit the following identifications:

Motion-producing substance	---	Crocin
"Fore-stage" V	---	cis-Crocetin dimethyl ester
"Final-stage" K_o	---	trans-Crocetin dimethyl ester

The copulation substances $K_♀$ and $K_♂$ were found to be mixtures of the "fore-stage" V and the "final-stage" K_o. For the female cells $K_♀$ is a mixture of three parts of the cis form V and one part of the trans form K_o. For the male cells $K_♂$ is a mixture of one part of the cis-isomer and three parts of the trans-isomer.

None of the three substances shown above is able to replace any of the others and, further, none may be replaced by any other substance. Even crocetin is without action.

SUMMARY

The copulation of the sex cells of the Chlamydomonas Eugametos proceeds in three steps:

	Treatment	Result	Due to Presence of
(1)	Short exposure	Flagellae become movable	crocin
(2)	Longer exposure	Female cells become capable of copulation	3 parts cis-crocetin dimethyl ester 1 part trans-crocetin dimethyl ester
(3)	Still longer exposure	Male cells become capable of copulation	1 part cis-crocetin dimethyl ester 3 parts trans-crocetin dimethyl ester

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Reported by W. H. Rieger
November 30, 1938

THE STRUCTURE AND SYNTHESIS OF MYOSMINE
AND N-METHYL MYOSMINE

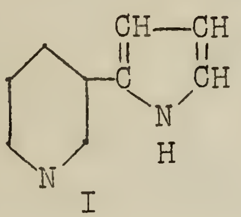
Spӓth -- University of Wien
Wibaut - University of Amsterdam

At least eight bases, similar to nicotine, have been found in tobacco smoke. Of these, myosmine is important in that, because of its odor, it contributes to the aroma.

Myosmine--Properties and Structure.--

Preliminary experiments disclosed the following:

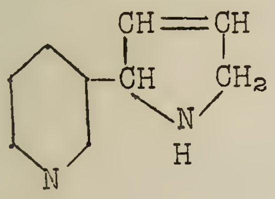
1. Weaker base than nicotine.
2. Color reactions with 2,4-dinitrochlorobenzene proved the presence of a pyridine nucleus.
3. Color with p-dimethylaminobenzaldehyde showed the absence of either a pyrrole or pyrrolidine ring.
4. Analysis gave the formula $C_9H_{10}N_2$, molecular weight 146. This together with the above evidence suggested a partially dehydrogenated nor-nicotine.
5. Dehydrogenation over Pd yielded 2-(beta-pyridyl)-pyrrole which had been isolated by Ehrenstein and shown to be:

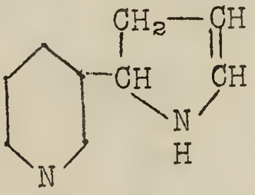

I

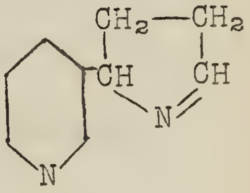
m.p. (picrate) 200°

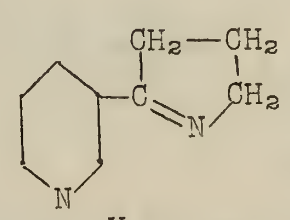
Dehydrogenation of l-nor-nicotine yielded the same product.

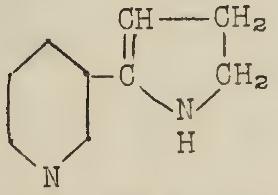
The following then are possible structures:


II


III

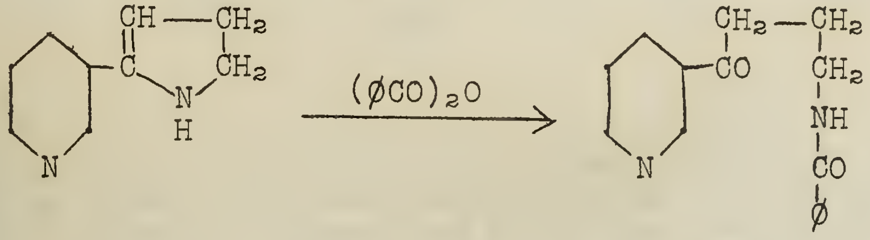

IV


V


VI

Since myosmine was shown to be optically inactive, formulas II, III and IV are excluded.

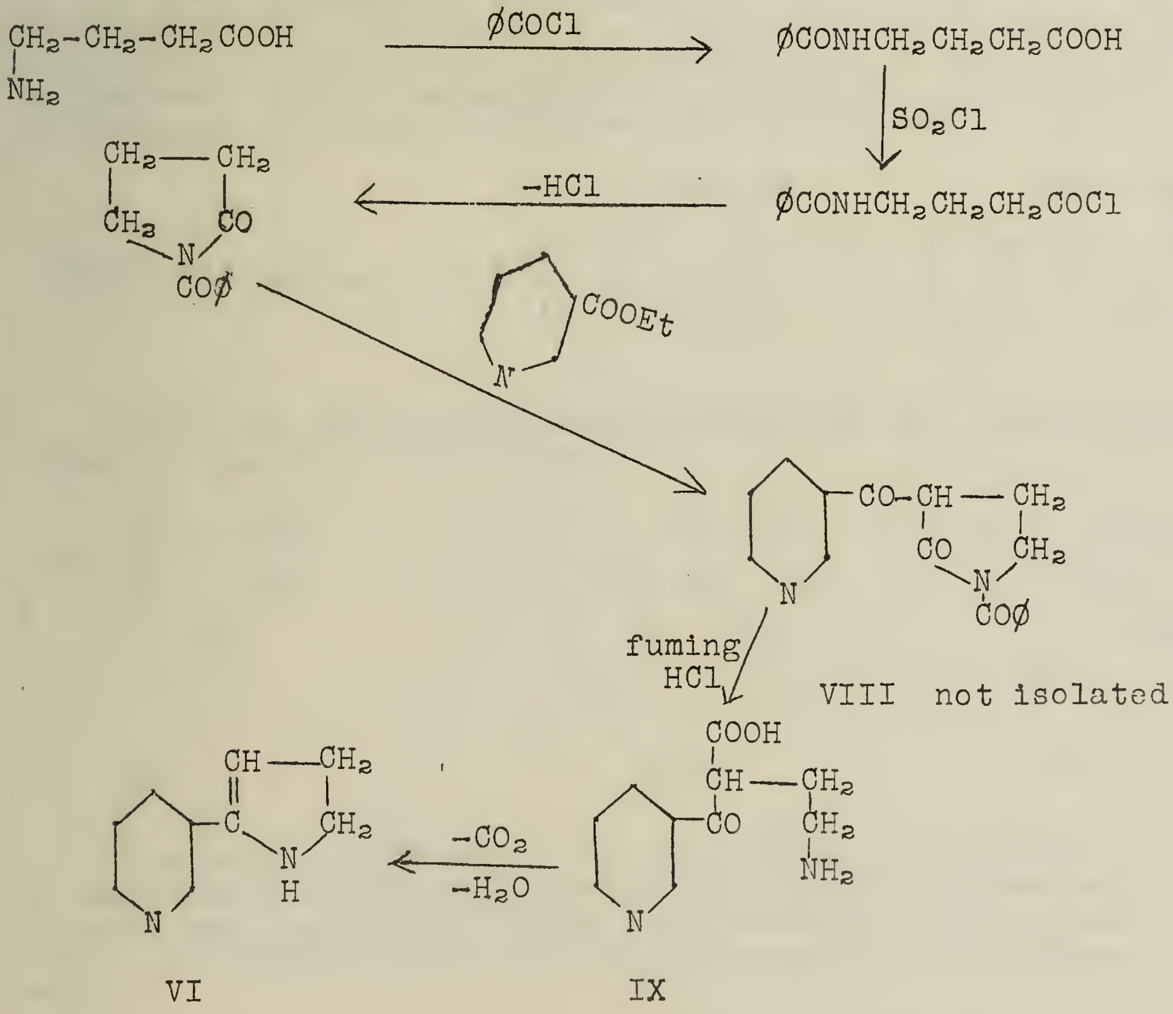
Treatment with benzoic anhydride in absolute ether yielded a benzoyl compound whose melting point was 118° and which on analysis gave the formula $C_{16}H_{16}O_2N_2$. Obviously this compound, VII, was not a simple benzoyl derivative but was formed, according to Späth, by cleavage of the pyrroline ring, followed by the addition of water.



VII

This last reaction favors formula VI although an equilibrium between V and VI was considered.

Myosmine--Synthesis.--

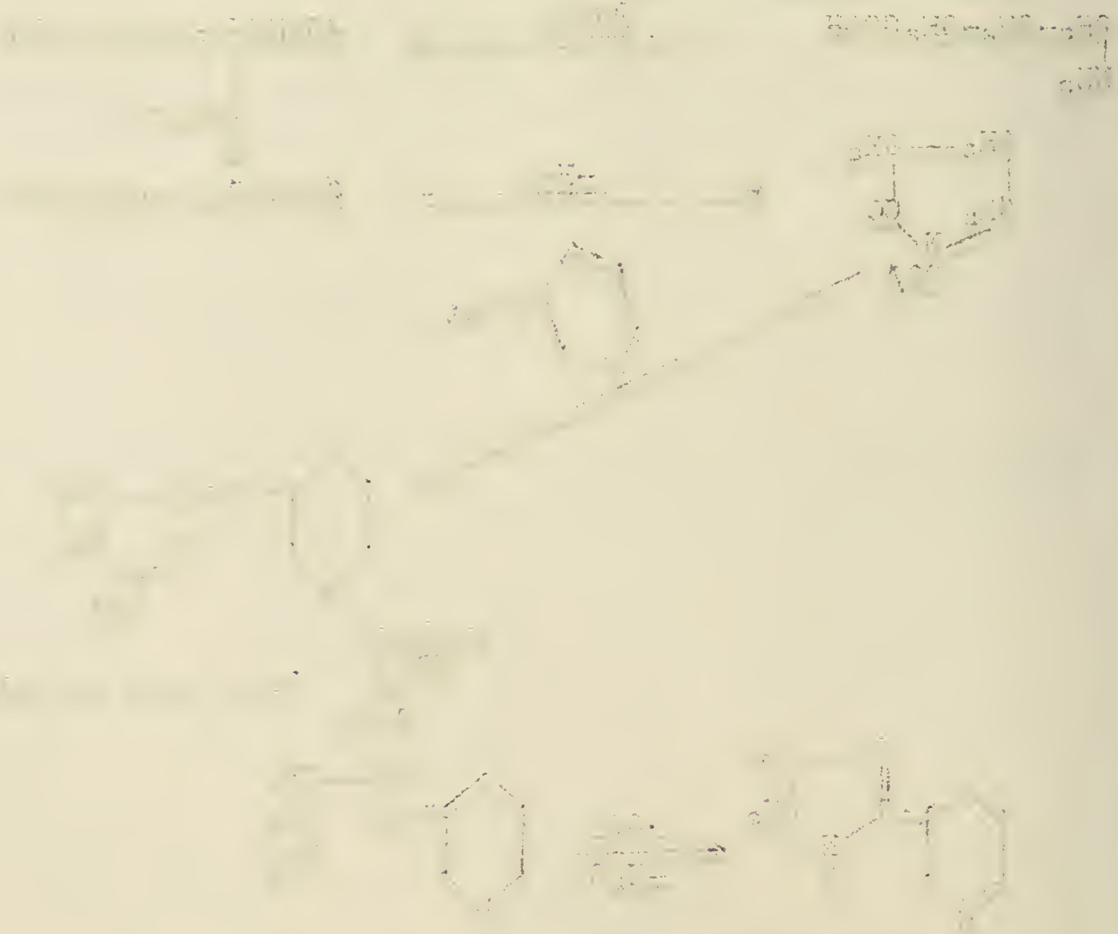


VI was obtained in 13 per cent yield and its picrate did not depress the melting point of the picrate of natural myosmine.

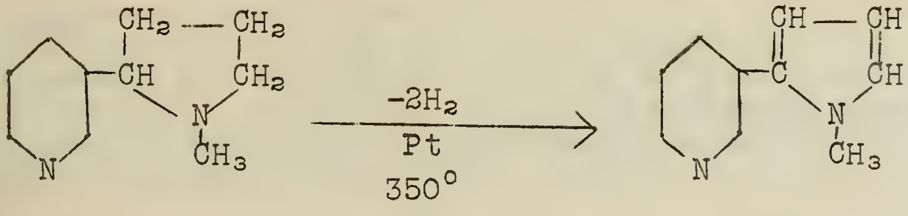
N-Methyl Myosmine--Structure.--Dehydrogenation of nicotine (X) over Pt yields nicotyrine (XI).

[illegible]

[illegible]

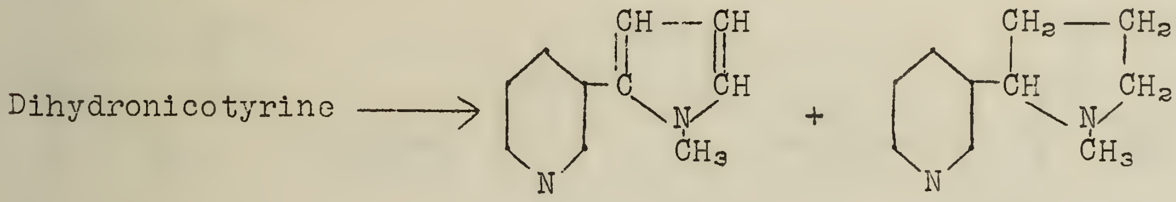


[illegible]

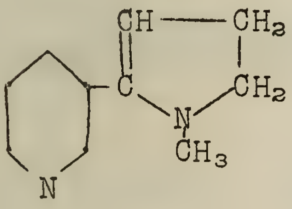


X XI

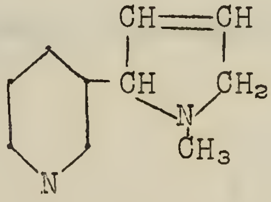
Treatment of XI with zinc and HCl yielded a compound $C_{10}H_{12}N_2$ which was basic to litmus and which definitely had an unsaturated structure. Nicotine up to 12 per cent yield was also obtained at the same time. Catalytic reduction (Pt) of XI in glacial acetic acid yielded a dihydronicotyrine, nicotine, dihydrometanicotine and some nicotyrine remained. The presence of nicotine in the first reaction is unexpected since it is very difficult to convert a pyrrole directly to a pyrrolidine, only one case of such a reduction ever being reported in the literature. Furthermore, nicotyrine (XI) is not to be expected in considerable amounts under the conditions of the catalytic reduction. The presence of both nicotine and nicotyrine is explained by a disproportionation reaction similar to the case of the rearrangement of cyclohexene and cyclohexadiene into benzene and cyclohexane observed by Zelinsky.



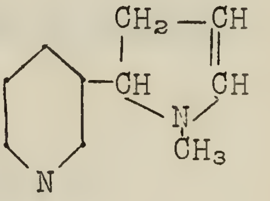
There are three possible structures for the dihydonicotyrine formed in the above reactions:



XII



XIII

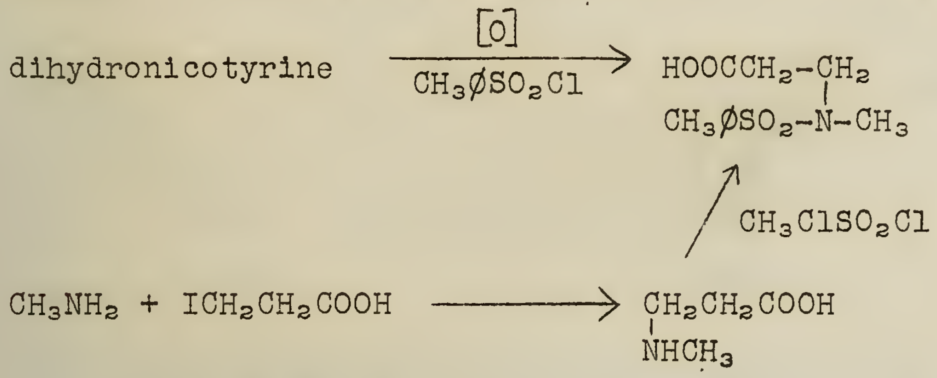


XIV

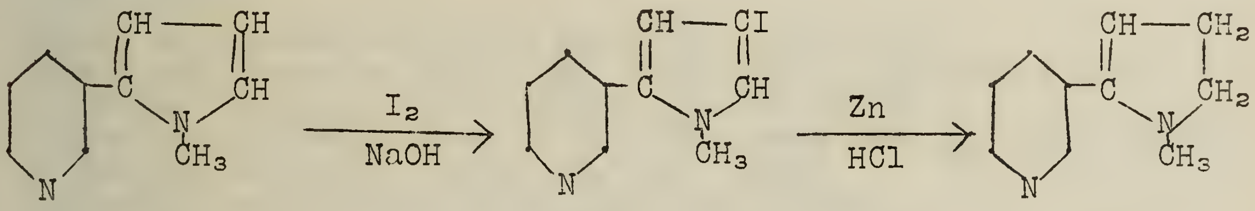
Oosterhuis and Wibaut, and later Späth and coworkers attempted to separate the dihydronicotyrine into optical isomers and obtained, in each case, a product with a small rotation. The results, however, were not conclusive due to the possible rearrangement noted above.

Späth then proved the structure to be XII by other methods: By mild oxidation of the dihydonicotyrine with potassium permanganate in sulfuric acid solution an N-methyl amino acid is to be expected;

from XII beta-N-methylaminopropionic acid, from XIII; N-methylamino acetic acid (Sarcosine); and from XIV no simple amino acid. The oxidation product was converted to its p-tolylsulfonyl derivative for identification. It did not depress the melting point of the p-tolylsulfonyl derivative of beta-N-methylaminopropionic acid synthesized by another method, m.p. 111°.


dihydronicotyrine
[O]
$CH_3ØSO_2Cl$
$HOOCCH_2-CH_2$
$CH_3ØSO_2-N-CH_3$
CH_3ClSO_2Cl
$CH_3NH_2 + ICH_2CH_2COOH$
CH_2CH_2COOH
$NHCH_3$

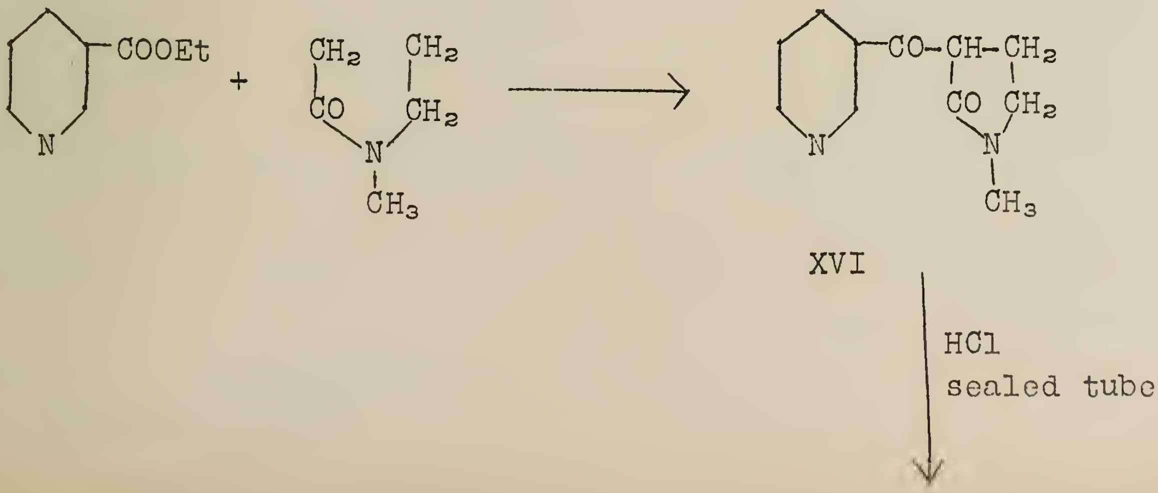
The product obtained by reduction of nicotyrine, therefore, has the structure XII, N-methyl myosmine. It is identical with the compound obtained by Pictet and Crepieux in 1898 who treated nicotyrine with iodine in sodium hydroxide solution and reduced this product with zinc and HCl:


CH
CH
C
CH
N
CH_3
N
I_2
NaOH
CH
CI
C
CH
N
CH_3
N
Zn
HCl
CH
CH_2
C
CH_2
N
CH_3
N

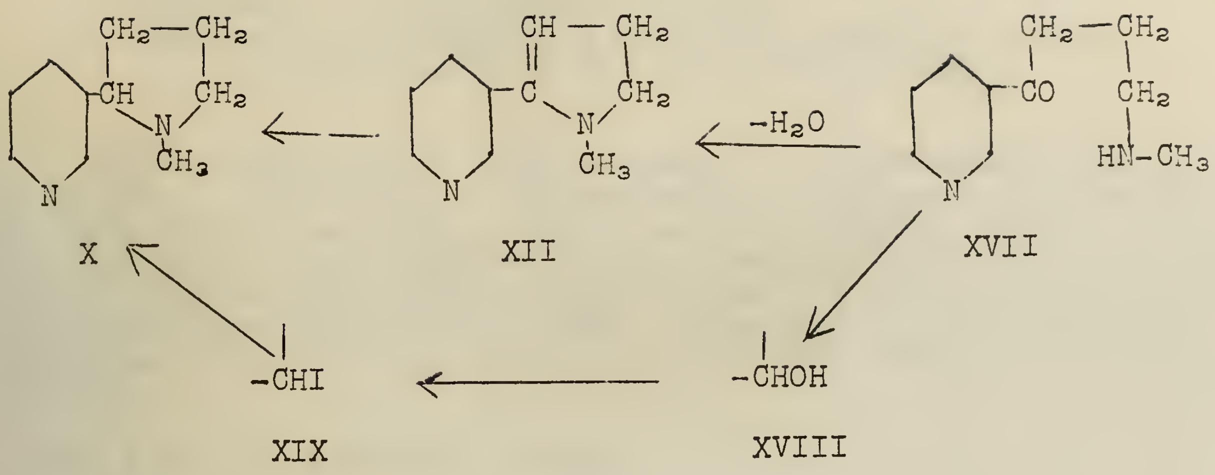
XV

XII

N-Methyl Myosmine--Synthesis and simplification of Späth's former synthesis of nicotine.--


COOEt
N
CH_2
CH_2
CO
CH_2
N
CH_3
N
CO-CH-CH_2
CO
CH_2
N
CH_3
HCl
sealed tube

XVI


CH₂—CH₂
CH
CH₂
N
CH₃
N
X
CH — CH₂
C
CH₂
N
CH₃
N
XII
-H₂O
CH₂—CH₂
CO
CH₂
HN-CH₃
N
XVII
-CHI
XIX
-CHOH
XVIII

The direct conversion of N-methyl myosmine into nicotine (and nicotyrine) eliminates the necessity of preparing the intermediate compounds XVIII and XIX.

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Wibaut and Overhoff, ibid., 47, 935 (1928)
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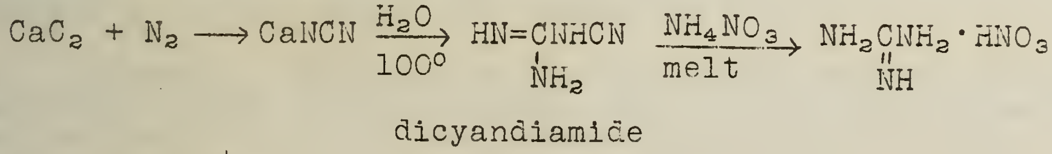
Reported by F. Richter
December 7, 1938.

Kazarian -- Erivan Polytechnic Institute, Armenia
Favorskii -- Leningrad University
Babajane -- Institute of Chemistry, Armenian Branch
of the Academy of Science of the U.S.S.R.

Calcium carbide was first prepared in considerable quantities by Moissan in the 1890's. Willson made it commercially available in 1892, using essentially the present-day method. Because of its low cost due to the cheapness of the starting materials, and because of its chemical properties, it has become one of the most important industrial raw materials of today. A partial list of important commercial products from calcium carbide with methods of preparation follows:

$$CaC_2 + 2H_2O \longrightarrow Ca(OH)_2 + C_2H_2$$

$$CaC_2 + 3HX \longrightarrow CH_2{=}CHX + CaX_2$$



$$CaC_2 + N_2 \longrightarrow CaNCN \xrightarrow[100^{o}]{H_2O} HN{=}\underset{\overset{|}{NH_2}}{C}NHCN \xrightarrow[melt]{NH_4NO_3} NH_2\underset{\overset{\|}{NH}}{C}NH_2\cdot HNO_3$$

dicyandiamide

$$C_2H_2 \xrightarrow[H_2SO_4]{HgSO_4^{+}} CH_3CHO$$

$$+\ CH_3COOH \longrightarrow CH_3CH(OCOCH_3)_2 \xrightarrow{\triangle} (CH_3CO)_2O + CH_3CHO$$

$$+\ HCl \text{ or } Cl_2 \longrightarrow \text{solvents}$$

$$+\ NH_4Cl + CuCl \longrightarrow CH_2{=}CHC{\equiv}CH + CH_2{=}CHC{\equiv}CCH{=}CH_2$$

$$+\ HgSO_4 + ClCH_2COOH \longrightarrow CH_2{=}CHOCOCH_2Cl \longrightarrow \text{polymer}$$

$$+\ CuCl_2 + HCl \longrightarrow CH_2{=}CHCl$$

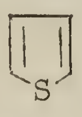
$$+\ CH_3COOH \longrightarrow CH_2{=}CHOCOCH_3 \longrightarrow \text{polymer}$$

$$+\ CH_3COCl \longrightarrow ClCH{=}CHCOCH_3$$

$$+\ C_2H_5OH \longrightarrow CH_3CH(OC_2H_5)_2$$

In addition, various compounds of synthetic interest can be prepared using calcium carbide or acetylene.

$C_2H_2 + S \longrightarrow$



$$+\ O_3 \longrightarrow \text{ozonides} \longrightarrow CHOCHO$$

$$+\ C_2H_5MgI + (C_2H_5)_2O \longrightarrow IMgC{\equiv}CMgI$$

$$+\ NaNH_2 \longrightarrow NaC{\equiv}CNa + NaC{\equiv}CH$$

$$C_2H_2 + Cu(NH_3)_2^+ \longrightarrow CuC{\equiv}CCu \longrightarrow HC{\equiv}C{-}C{\equiv}CH$$

$$CaC_2 + F_2 \longrightarrow CaF_2 + CF_4 \ (25^\circ)$$

$$+ Br_2 \longrightarrow CaBr_2 + C_2Br_6 \ (25^\circ\text{, stand five months})$$

$$+ I_2 \longrightarrow CI_2{=}CI_2 + IC{\equiv}CI \ (170^\circ)$$

In general, calcium carbide may function in a reaction in three different ways: (1) as a dehydrating agent, (2) as a catalyst, (3) as an organo-metallic compound. All these functions are interrelated, in all probability.

Calcium carbide has been used as a drying agent for alcohol, and it is claimed that the method possesses some advantages over other means. A small amount of anhydrous $CuSO_4$ must be added to absorb the acetylene and the various impurities present in the carbide. In some other reactions it may or may not act as a dehydrating agent. These are considered later.

If phenol, alcohols, or halogen derivatives of hydrocarbons are heated with calcium carbide under 12-40 atmospheres pressure and at 150-300°, acetylenic hydrocarbons result. Thus

$$C_2H_5OH \longrightarrow C_2H_5C{\equiv}CC_2H_5$$

$$C_6H_5\underset{(OH)}{Cl} \longrightarrow C_6H_5C{\equiv}CC_6H_5$$

The acetylenic hydrocarbons may easily be hydrogenated to the saturated compounds if desired.

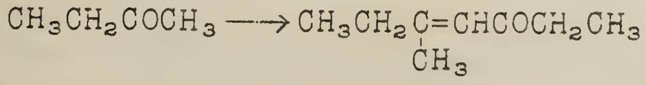
The α and β dichlorotolanes can be prepared by treating CaC_2 with a benzene solution of chlorine.

$$2C_6H_6 + 2Cl_2 + CaC_2 \longrightarrow C_6H_5CCl{=}CClC_6H_5 + CaCl_2 + 2HCl.$$

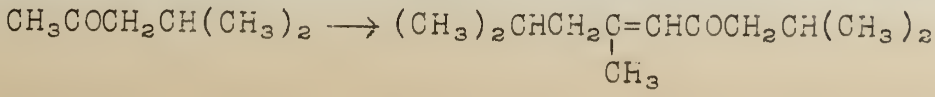
Under proper conditions, the tetrachloro compound can also be isolated.

Certain active methylene compounds will form the metal derivatives with calcium carbide. Among them are CH_3COCH_2COOR, $CH_3COCH_2COCH_3$, $C_2H_5OCOCOCH_2COOR$, $NCCH_2COOR$, $NCCH_2CN$. Malonic ester, benzyl cyanide, and fluorene do not react. Ketones containing the $-COCH_3$ group react to give various products by the elimination of water. The chief product is that resulting from a bimolecular condensation.

$$CH_3COCH_3 \longrightarrow (CH_3)_2C{=}CHCOCH_3$$

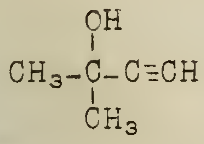


$$CH_3CH_2COCH_3 \longrightarrow CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}{=}CHCOCH_2CH_3$$

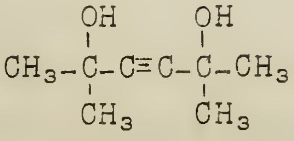


$$CH_3COCH_2CH(CH_3)_2 \longrightarrow (CH_3)_2CHCH_2\underset{\displaystyle CH_3}{\underset{|}{C}}{=}CHCOCH_2CH(CH_3)_2$$

In 1934, Kazarian discovered that acetylenic alcohols could be prepared by allowing calcium carbide to react with ketones in the presence of base. The reaction was carried out using acetone, and gave two products:



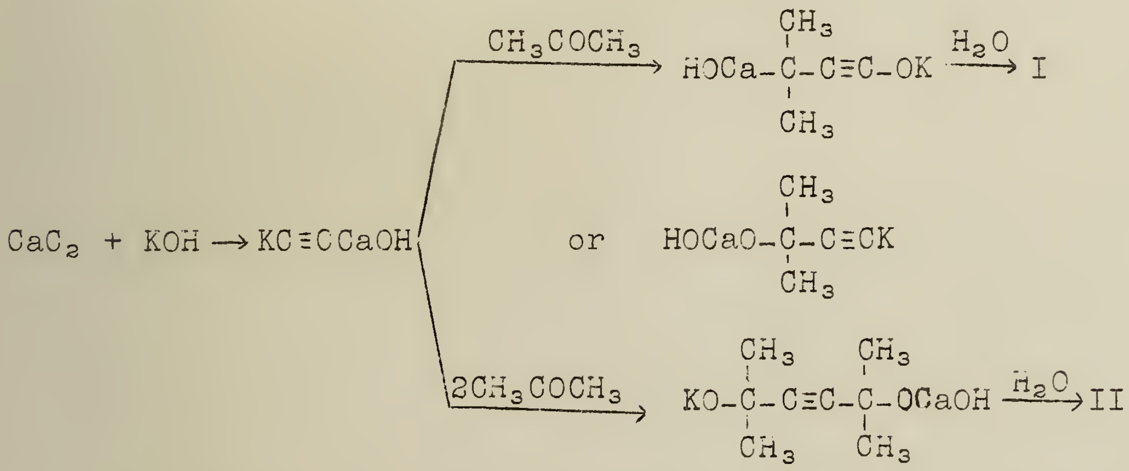
$$CH_3-\overset{OH}{\underset{CH_3}{C}}-C\equiv CH$$



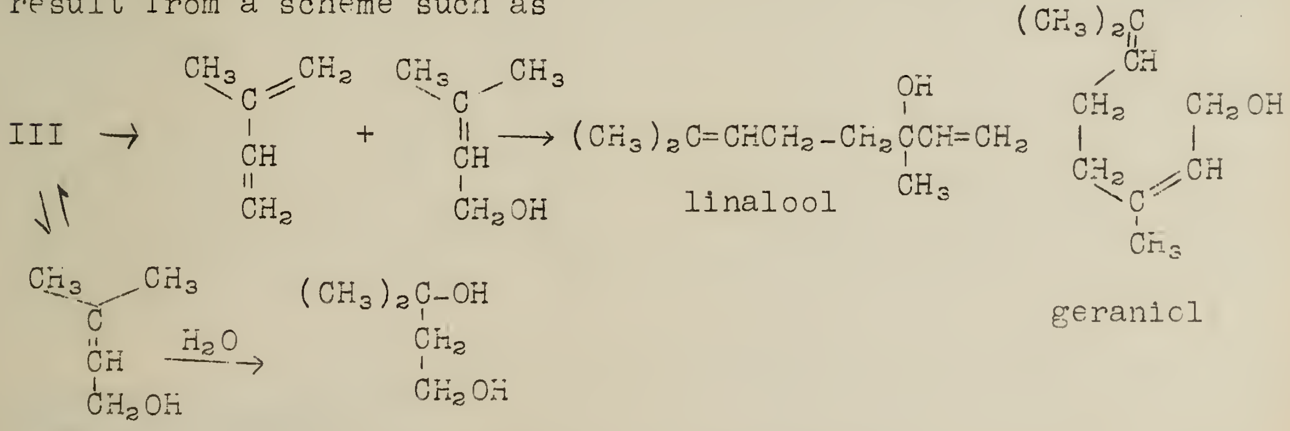
$$CH_3-\overset{OH}{\underset{CH_3}{C}}-C\equiv C-\overset{OH}{\underset{CH_3}{C}}-CH_3$$

dimethylethinylcarbinol (I) 2,5-dimethylhexyne-3-diol-2,5 (II)

The suggested mechanism for the reaction is:


CaC₂ + KOH → KC≡CCaOH
CH₃COCH₃
HOCa-C(CH₃)₂-C≡C-OK
H₂O
I
or
HOCaO-C(CH₃)₂-C≡CK
2CH₃COCH₃
KO-C(CH₃)₂-C≡C-C(CH₃)₂-OCaOH
H₂O
II

By varying the conditions, either I or II could be obtained in 70 per cent yield. I can be hydrogenated to give dimethylvinylcarbinol (III), which when treated with 20 per cent H_2SO_4 gives a complex mixture of products of which the following were isolated and characterized: Isoprene, dimethylvinylcarbinol, isobutenylcarbinol, linalool, and dimethyltrimethyleneglycol. The odor of geraniol was noticed during the distillation, but was not isolated. These could result from a scheme such as


III
CH₃ CH₂ C CH CH₂
+
CH₃ CH₃ C CH CH₂OH
(CH₃)₂C=CHCH₂-CH₂C(OH)(CH₃)CH=CH₂
linalool
(CH₃)₂C CH CH₂ CH₂ C CH₃ CH CH₂OH
geraniol
CH₃ CH₃ C CH CH₂OH
H₂O
(CH₃)₂C-OH CH₂ CH₂OH

These methods give promise of being possible means for the synthesis of isoprene and terpene derivatives.

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Reported by L. C. Behr
December 7, 1938

REACTION MECHANISM OF MARCKWALD'S "ASYMMETRIC SYNTHESIS"

THE ASYMMETRIC INDUCTION OF E. ERLENMEYER

RESOLUTION OF RACEMATES BY MEANS OF MOLECULAR COMPOUNDS

Fritz Eisenlohr and Gerhard Meyer
University of Königsberg

In 1904 Marckwald decomposed the solid acid brucine salt of methyl ethyl malonic acid by heating to 170°. He obtained the brucine salt of methyl ethyl acetic acid which, upon acidification and steam distillation, yielded a free methyl ethyl acetic acid with an $[\alpha]_D = -17.8^\circ$, corresponding to an excess of about 10 per cent of the *l*- over the *d*-form.

As to what part of the process is responsible for the formation of an optically active final product, opinions differ widely. In agreement with Marckwald, Eisenlohr and Meyer found that the rotation of the end product is the same whether the brucine salt is crystallized from methanol, ethanol, or acetone. After ten fractional crystallizations of the salt from methanol, the first and last fraction gave the same rotation.

Erlenmeyer, Jr., attempted to explain this synthesis by his asymmetric induction theory. Ebert and Kortüm have already proven most of his other applications of the theory to be incorrect. They suggested that the rotation of his valeric acid might be due to the presence of a small amount of tartaric ester (Erlenmeyer had used tartaric acid in place of brucine). Eisenlohr and Meyer repeated Erlenmeyer's work, taking extra precautions to rid the valeric acid of ester impurities. The end product was inactive. This removes the last experimental support of Erlenmeyer's theory.

Marckwald himself suggested that the brucine salt was obtained in only one form since there was a slight difference in the solubility of the two forms. He further assumed that rearrangements and partial racemization took place to explain the low rotation of the final product. Eisenlohr and Meyer carried out the following series of experiments which disproved this and other guesses and which led to the discovery of an explanation which will agree with all the experimental work.

(1) Eisenlohr and Meyer studied the rate of decomposition and its effect on the final rotation. At 180-200° the decomposition was complete in three minutes. At 140-150° the time was three hours. Yet in both cases the final rotation was the same. This result practically excludes the possibility of racemization and also the possibility of a difference in decomposition rates of the two forms.

(2) It was observed that the evolution of CO_2 ceased when the last crystals disappeared. This raised the question as to whether the decomposition proceeds in the same way when the salt is noncrystalline or in solution. The salt may be obtained in a viscous noncrystalline form from an alcoholic solution containing only half the calculated amount of brucine. If immediately decomposed, this preparation gave an optically inactive product. If the preparation was allowed to crystallize the product was again active.

If the salt is dissolved in pyridine, benzaldehyde, or acetophenone and decomposed in solution, the product is inactive.

There seems to be only one conclusion that can be reached. In the noncrystalline state or in solution the two diastereoisomers are present in equal amounts and both decompose at the same rate. To substantiate this further the acid strychnine, nicotine, and chinchonine salts were made. These showed no tendency to crystallize and the final decomposition product was inactive. *d*- and *l*-Methylbornylamine yielded well crystallized salts of the malonic acid. On decomposition, only one-fourth of the calculated amount of CO_2 had been given off when the salt was completely fused. Further heating caused complete decomposition. As expected, the final product was inactive.

(3) The acid brucine salt of methyl phenyl malonic acid was made. The methyl phenyl acetic acid obtained from the salt gave a positive rotation under the same conditions which had given a methyl ethyl acetic acid with a negative rotation before. Ethyl benzyl acetic acid, derived from the brucine salt of the corresponding malonic acid, also had a positive rotation. Eisenlohr and Meyer conclude that in the separation of the acid brucine salts in the crystalline form there occurs a shifting in the equilibrium of the two diastereoisomers, corresponding to their different solubilities.

Very few cases are known of the resolution of a racemate through molecular compounds. A racemate should be best adapted to resolution by this means when the components are present as a racemic mixture or as racemic mixed crystals. Otherwise it might be expected that the tendency of the *d*- and *l*-forms to combine with each other would hinder the formation of a molecular compound with a third substance. Eisenlohr and Meyer have studied several systems by the thaw-fusion diagram method. With a single exception, all the seemingly promising systems investigated proved disappointing either because contrary to the statements in the literature they formed no molecular compounds, or because the compound could not be decomposed into the optical antipodes. The following nine systems were investigated:

(1) *d*-Camphor and *l*-menthol
Eutectic at 58 mole per cent camphor and 8°

(2) *d*-Mandelic acid and *d*-camphor
Eutectic at 74 per cent acid and 60°

(3) Menthol and *d*-citronellal
The exact composition of the eutectic could not be determined because the citronellal in large excess solidifies in the glassy form. The eutectic must lie very far on the citronellal side; no compound is formed.

(4) *d*-Camphor and *d*-citronellal
There is an inflection in the curve at 46 per cent camphor and -20°, indicating an unstable molecular compound. The most varied

crystallization gave only solid camphor with traces of citronellal.

(5) d-Camphor and 3-hydroxy-4-methoxy mandelic acid
These two were tried because it had been reported previously that camphor and salicylic acid formed a molecular compound. Upon investigation it was found that neither pair formed a compound.

(6) d-Camphor and resorcylmethylcarbinol
Camphor and resorcinol form a 1:1 molecular compound, but the above pair forms only a mixture.

(7) d-Carvone and d-chinchonine

(8) d-Camphor and d-chinchonine
Neither pair forms a compound.

(9) d-Amygdalin and menthol
These were chosen because of Windaus' success in resolving racemates with digitonin. These two formed a 1:1 compound. Recrystallization of the molecular compound was impossible because of the insolubility of amygdalin in organic solvents and, therefore, no resolution could be affected.

The system resorcylmethylcarbinol brucine cannot be studied by the above method because both components undergo change on fusion. When they are dissolved in methanol a product separates out, the rotation of which changes on continued fractional crystallization indicating the possibility of resolution. Analysis showed the compound to have a 1:1 ratio of its components. Eisenlohr and Meyer succeeded in resolving the carbinol by means of this compound. Another possible method of determining whether or not binary systems form compounds is to measure their dielectric constants. Curves for 0.2 M dioxane solutions of the following five systems were studied:

(1) d-Camphor-salicylic acid
No compound

(2) d-Camphor-resorcinol
1:1 compound

(3) Brucine-resorcylmethylcarbinol
1:1 compound

(4) Brucine-menthol
No compound

(5) Brucine-β-phenyl-ethyl alcohol
No compound

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Eisenlohr and Meyer, Ber., 71, 997 (1938); 1004 (1938); 1005 (1938)
Ritchie, Asymmetric Synthesis and Asymmetric Induction.
The first three references give an additional twenty-five references.

Reported by A. W. Anderson
December 14, 1938

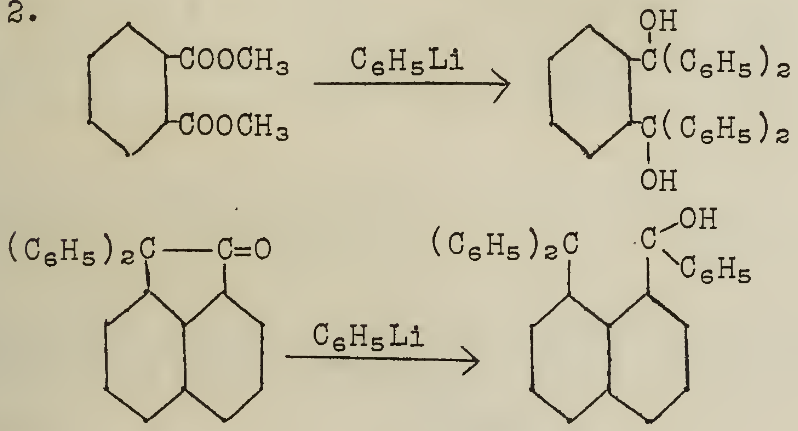
REPLACEMENT OF AROMATIC HYDROGEN BY LITHIUM

Wittig, Pockels and Dröge--Chemical Institute
of the Baaunschweig
Technical High School
and the University
of Freiburg.
Challenger and Miller--University of Leeds

I. A general survey of the uses of organo-lithium compounds. The following are examples of the more important reactions of lithium compounds, which are useful in organic syntheses.

1. $C_6H_5Cl + 2\ Li \longrightarrow C_6H_5Li + LiCl$

2.



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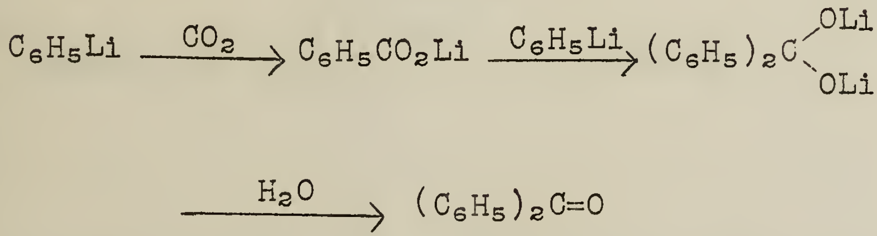
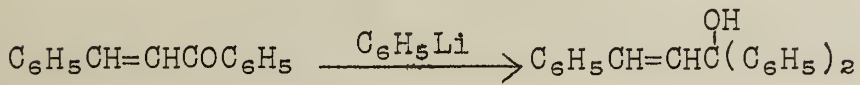


$$C_6H_5Li \xrightarrow{CO_2} C_6H_5CO_2Li \xrightarrow{C_6H_5Li} (C_6H_5)_2C\begin{smallmatrix}OLi\\OLi\end{smallmatrix} \xrightarrow{H_2O} (C_6H_5)_2C{=}O$$

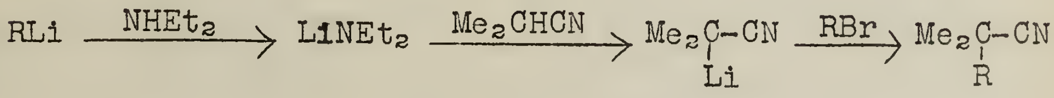
4.



$$C_6H_5CH{=}CHCOC_6H_5 \xrightarrow{C_6H_5Li} C_6H_5CH{=}CH\overset{OH}{C}(C_6H_5)_2$$

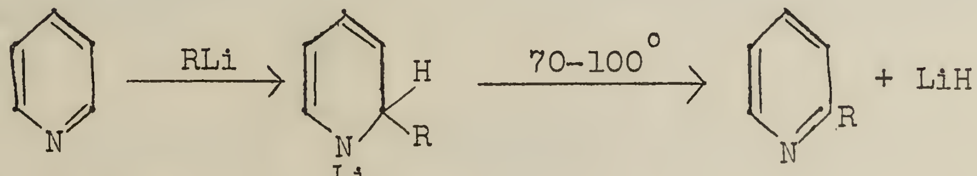
5. $RLi + NHEt_2 \longrightarrow LiNEt_2 + RH$

6.

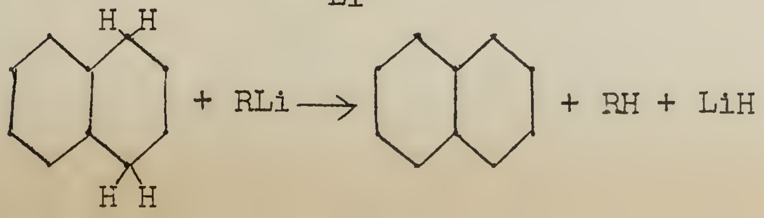


$$RLi \xrightarrow{NHEt_2} LiNEt_2 \xrightarrow{Me_2CHCN} Me_2\underset{Li}{C}{-}CN \xrightarrow{RBr} Me_2\underset{R}{C}{-}CN$$

7.



8.



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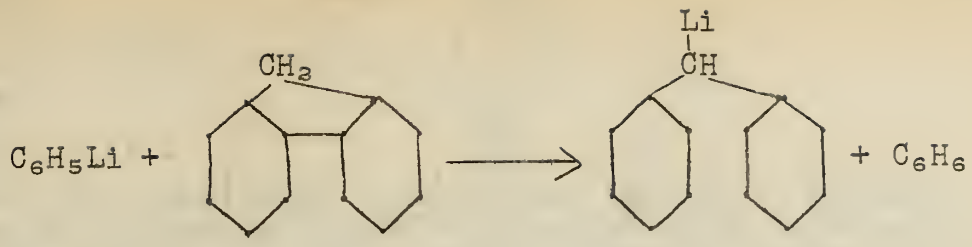
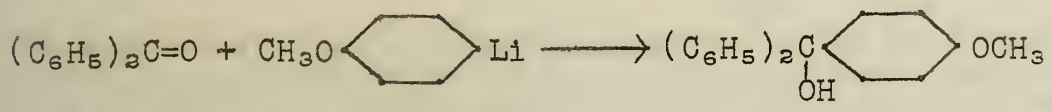
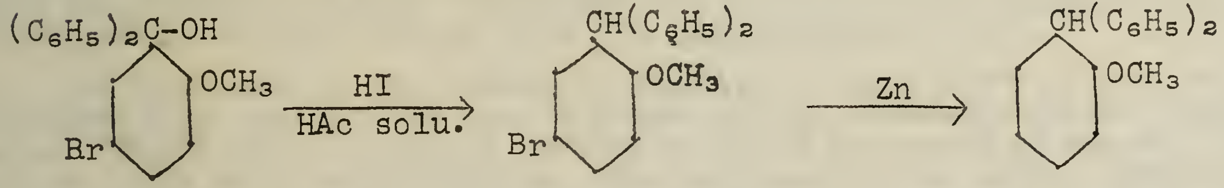


II. Replacement of aromatic hydrogen by lithium.

For the synthesis of certain carbinols, a few esters of dicarboxylic acids were treated with *p*-lithiumanisole, prepared from *p*-bromoanisole and lithium in absolute ether according to the directions of Gilman. The reaction of *p*-lithiumanisole with the esters took an unexpected course and doubt arose as to the composition of the reagent. Treatment of the lithium compound with benzophenone should give diphenylanisylcarbinol.



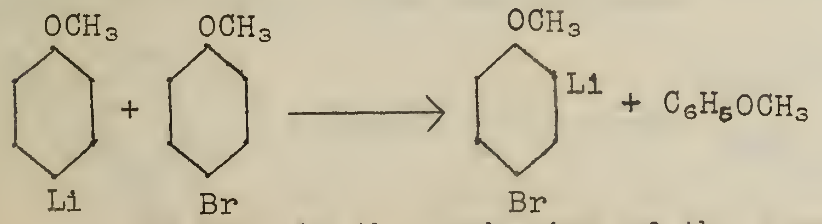
Instead, a bromine-containing carbinol was obtained whose structure is represented by I. This substance was converted



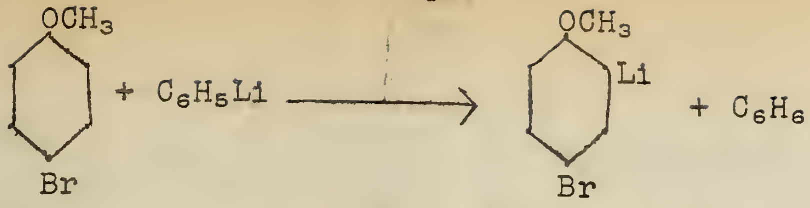
I II III

to the known compound (III) which was identified by a mixed melting point determination. Compound I was synthesized from an *o*-methoxy benzoic ester and phenylmagnesium bromide, followed by bromination of the resulting carbinol.

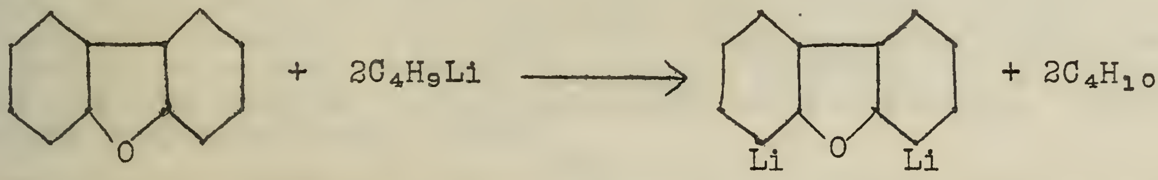
This shows that the action of lithium on *p*-bromoanisole results in *o*-lithium-*p*-bromoanisole. The question now arises as to the origin of this compound. If one disregards the improbable direct substitution of the hydrogen atom by lithium, the following explanation is most probable. First, the normal reaction occurs, forming *p*-lithiumanisole, which then reacts further with the *p*-bromoanisole present.



If this is the mechanism of the reaction, then other organolithium compounds should also transform *p*-bromoanisole into *o*-lithium-*p*-bromoanisole. This was confirmed using phenyllithium. The reaction is practically complete in twenty-four hours.



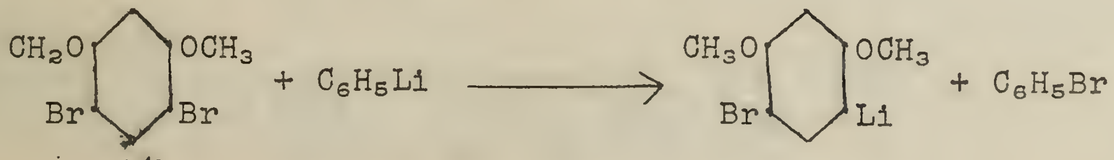
This reaction was then tried using anisol instead of *p*-bromoanisole. No sign of conversion could be detected after twenty-four hours at room temperature. At 100° a marked reaction occurs, which is complete in four hours. Addition of benzophenone gave diphenyl-*o*-methoxycarbinol in 68 per cent yield. It is noteworthy here that the lithium enters the anisol in the *ortho* position. This finding corresponds entirely to that of Gilman and Young, who found that when the lithium atom enters diphenyl oxide it takes the 1,8- and not the 3,6-positions.



The replaceability of aromatic hydrogen atoms by lithium can be traced back to a polarization of the carbon-hydrogen bond through the influence of negative substituents, such as methoxyl and bromine. This acidifying effect dries out with increasing distance from the substituent, just as the dissociation constants of the halogenated fatty acids become less with increasing distance between the halogen atom and the carboxyl group. The metal atom replaces the *ortho*-hydrogen atom, as it is more acidic than the *para*-hydrogen atom.

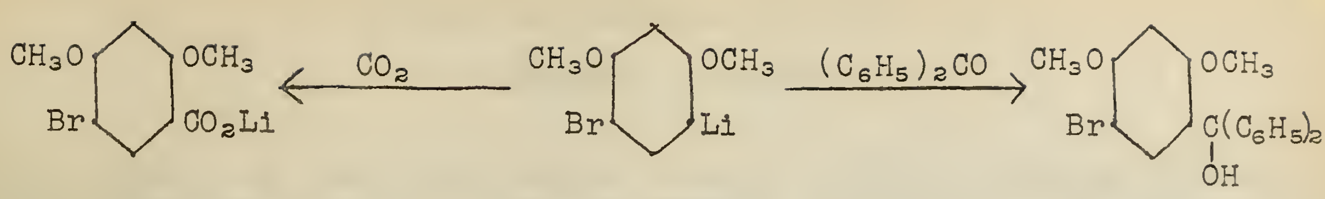
An increase in the number of negative substituent groups on the benzene ring facilitates the entrance of the electropositive lithium atom. While anisole itself is not acted on by standing several days in the cold with phenyllithium, the replacement is nearly complete after sixty hours with hydroquinone dimethyl ether and resorcinol dimethyl ether. *p*-Bromoanisole is converted more rapidly than hydroquinone dimethyl ether. This is attributed to the stronger acidifying effect of the bromine atom in comparison with the methoxyl group. The lithium atom enters in the position *ortho* to the methoxyl and not to the bromine, due possibly to the steric effects of the large bromine atom.

Finally, the behavior of dibromoresorcinol dimethyl ether with phenyllithium was investigated. Since this compound contains twice as many negative groups as *p*-bromoanisole, an especially great reactivity was expected. The reaction was complete in a few minutes, but it took a different course. By hydrolysis a 97 per cent yield of monobromoresorcinol dimethyl ether and a nearly equivalent amount of bromobenzene (73 per cent) was obtained, instead of the expected dibromoresorcinol dimethyl ether and benzene.



IV

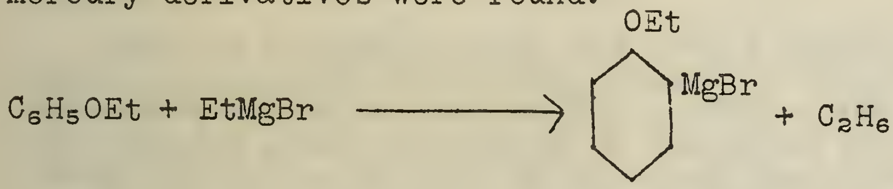
This interchange of bromine and lithium atoms has not been observed before. However, the reaction was tried repeatedly and takes place rapidly with the formation of appreciable amounts of by-products. The structure of compound V was determined by the use of benzophenone

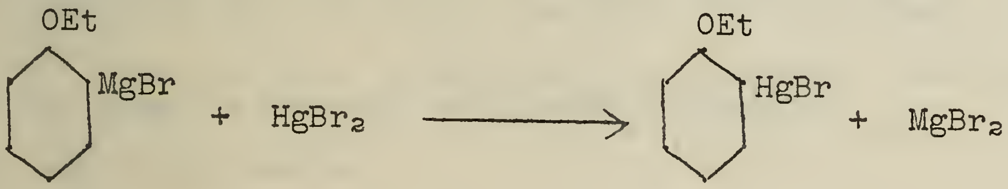


V

III. Comparison with Grignard reagents.

In carrying out certain reactions using Grignard reagents in boiling phenetole, Challenger and Miller found products which seemed to indicate that the MgBr group had replaced hydrogen in the aromatic nucleus. To confirm this ethylmagnesium bromide was allowed to react with boiling phenetole. Treatment of the product with mercuric bromide yielded o-phenetyl mercury bromide. No other mercury derivatives were found.





The reaction was then extended to anisole. Ethylmagnesium bromide was used, and after treatment with mercuric bromide, only o-anisylmercury bromide was isolated. n-Propylmagnesium bromide gave the same result. It was shown in separate experiments that phenetole and anisole are not mercurated by boiling with ethereal solutions of mercuric bromide.

These results indicate that substitution of the -MgBr group for hydrogen in anisole occurs exclusively in the ortho position. This was confirmed by a careful fractional crystallization of the products from two separate experiments with anisole and ethylmagnesium bromide. Only o-anisylmercury bromide and some ethyl mercury bromide could be isolated. The yields in these reactions were small.

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Reported by E. M. Bottorff
December 14, 1938

THE USE OF NITROSYL CHLORIDE
IN ORGANIC CHEMISTRY

There are few known compounds which provide a greater variety of reactions than NOCl does, as regards simplicity of structure and resistance to decomposition by physical agencies. Furthermore, few organic or inorganic compounds fail to react with NOCl in some way or other.

NOCl has been prepared in a variety of ways all depending upon the reaction of chlorine or a chloride with an oxide or acid of nitrogen or with some simple nitrogen derivative. Undoubtedly most methods are meritorious for individual cases, but the best practical methods for general use are the reaction of nitrosyl sulfate upon NaCl and the reaction of concentrated HCl upon an alkyl nitrite (usually ethyl or amyl nitrite).

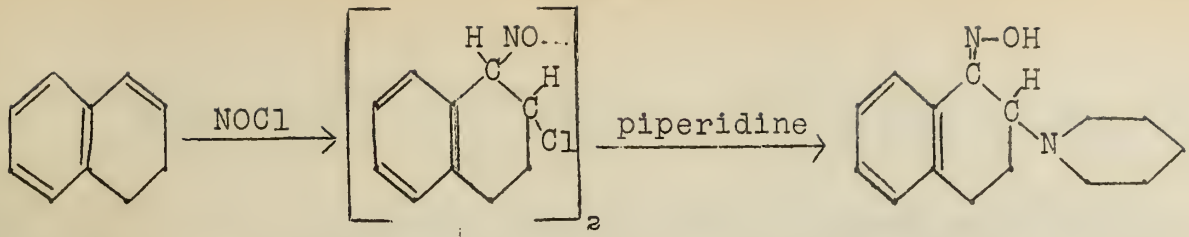
NOCl is a reddish-brown gas with a characteristic odor, condensing to a dark red liquid boiling at -5.8°C and solidifying to blood-red crystals, m.p. -60° to -61°C. NOCl is unassociated in the gaseous state and starts to decompose into NO and Cl_2 only above 700°C, being about 50 per cent dissociated at 985°C. It is seen that NOCl is one of the most stable nitrogen compounds.

The reactions of NOCl will be discussed according to the type of organic compound with which it reacts:

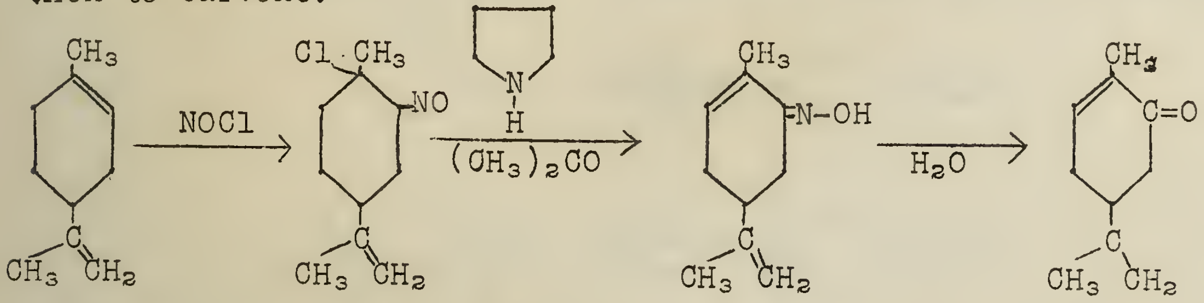
A. Hydrocarbons

1. Unsaturated

(a) Ethylenic hydrocarbons (including the terpenes) react with NOCl by the latter adding to the double bond to form the nitroso chloride. Nitroso compounds characterized by the -NO group were first prepared by Cahours in 1842. The discovery by Tilden, in 1875, that they could be prepared by the addition of NOCl to unsaturated compounds, and the subsequent improvement in the method by Wallach, in 1888, first placed nitroso compounds in the important position they now hold. In the addition of NOCl to unsaturated compounds a blue coloration appears first, which is ascribed to the nitroso compound itself, but soon fades and the final compounds are generally colorless. The latter have been shown to be isonitroso (=N-OH) or bisnitroso ($R-N_2O_2-R$) compounds. Sidgwick in his book "Organic Chemistry of Nitrogen" gives an extended discussion of the theories of the structure of bisnitroso compounds. Straus and Ekhard have observed the formation of the bisnitrosochloride from 1,2-dihydronaphthalene and the former's transformation into the nitrolamine with piperidine:



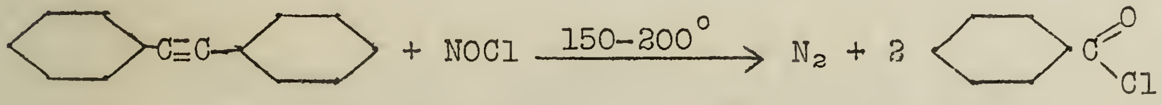
Wallach has observed the addition of NOCl to limonene to form limonene nitrosochloride which was transformed to carvoxime and then to carvone:



The above reaction has been universally used for identification of terpenes.

Tilden found that addition of NOCl also occurred with unsaturated acids and aromatic-aliphatic ethers which had unsaturated side-chains.

(b) Acetylenic hydrocarbons have not been very thoroughly studied, but Perrot found that diphenylacetylene (tolane) reacted as follows:



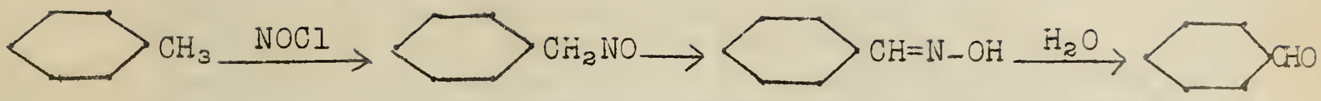
At lower temperatures chlorinated and nitrosated products resulted.

2. Saturated

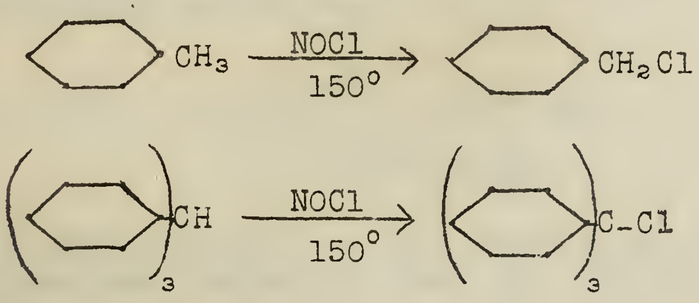
Lynn first noted the reaction of NOCl with saturated hydrocarbons in 1919. He found that a solution of *n*-heptane, when saturated (3 per cent) with NOCl and placed in sunlight, developed a blue coloration which slowly faded out with subsequent precipitation of a brown oil. The latter was steam distilled, and then the distillate was fractionated giving mostly dipropyl ketone with small amounts of methyl-butyl ketones.

Mitchell and Carson furthered this work by obtaining approximately equal amounts of methyl-butyl and ethyl-propyl ketones from a similar treatment of *n*-hexane.

Lynn was also able to obtain benzaldehyde from toluene by reaction of NOCl in sunlight. He proposed the following mechanism:



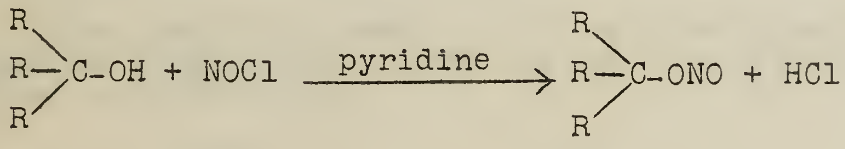
Recently Perrot (1934) observed that certain saturated hydrocarbons could be chlorinated by use of NOCl if the two compounds were heated to 150° in tubes sealed *in vacuo*. Examples of this type of reaction are:



B. Alcohols, phenols, and mercaptans

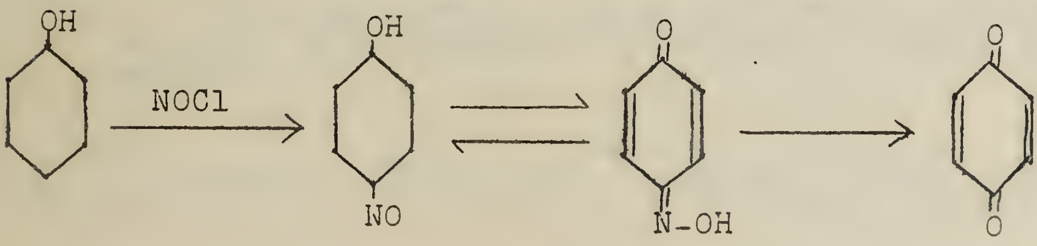
Lee and Lynn found that all aliphatic alcohols gave nitrites when treated with NOCl. Tertiary and high molecular weight alcohols must also have pyridine or a similar reagent added in order to facilitate splitting out of HCl. These reactions may be illustrated as follows:

$$R\text{-}OH + NOCl \longrightarrow RONO + HCl$$



$$R_3C\text{-}OH + NOCl \xrightarrow{\text{pyridine}} R_3C\text{-}ONO + HCl$$

Thymol and certain substituted phenols give nitroso derivatives upon NOCl treatment; while phenol, itself, is transformed into benzoquinone. This latter reaction was originally thought due to the oxidizing ability of NOCl but has been more recently explained by the following mechanism:



Mercaptans react with NOCl in the following manner:

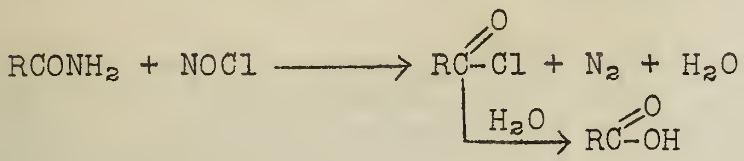
(1) $2NOCl + RSH \longrightarrow 2HCl + 2NO + R_2S_2$

(2) $NOCl + RSH \longrightarrow HCl + RSNO$

Reaction 1 is general for all except the tertiary mercaptans where 2 becomes the predominant reaction due to the relative increase in stability of the "thionitrite" formed. These reactions are carried out at low temperatures; under such conditions triphenylmethyl mercaptan has been transformed in 90 per cent yield to triphenylmethyl thionitrite.

C. Amines and amides

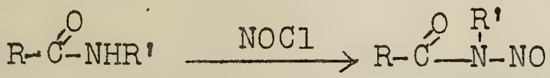
Tilden and Forester have found that amides, in general, react with NOCl as follows:



$$\mathrm{RCONH_2 + NOCl \longrightarrow R\overset{O}{\overset{\|}{C}}{-}Cl + N_2 + H_2O}$$

$$\mathrm{R\overset{O}{\overset{\|}{C}}{-}Cl \xrightarrow{H_2O} R\overset{O}{\overset{\|}{C}}{-}OH}$$

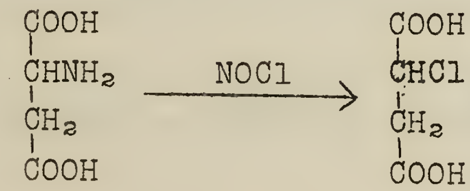
Monosubstituted amides, on the other hand, react in the same way as secondary amines to form the corresponding nitroso compound:



$$\mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}NHR' \xrightarrow{NOCl} R{-}\overset{O}{\overset{\|}{C}}{-}\overset{R'}{\overset{|}{N}}{-}NO}$$

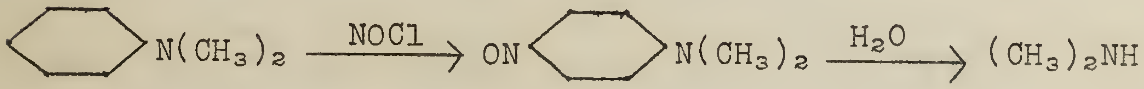
NOCl has been used quite frequently in replacing amino groups by chlorine, especially in the transformations of optically active compounds. A study of such reactions has been made by Zemplen and Csuros with the exception that NOBr was used in place of NOCl. They found that the replacement of NH_2- by Br- was only effected in α- and β-amino acids.

The classical example of this transformation was the changing of *l*-aspartic acid into *l*-chlorosuccinic acid by Tilden and Marshall:

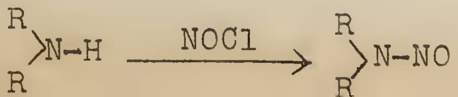


$$\begin{array}{c} \mathrm{COOH} \\ | \\ \mathrm{CHNH_2} \\ | \\ \mathrm{CH_2} \\ | \\ \mathrm{COOH} \end{array} \xrightarrow{\mathrm{NOCl}} \begin{array}{c} \mathrm{COOH} \\ | \\ \mathrm{CHCl} \\ | \\ \mathrm{CH_2} \\ | \\ \mathrm{COOH} \end{array}$$

NOCl can also be used in nitrosating disubstituted anilines with subsequent hydrolysis to obtain secondary amines:



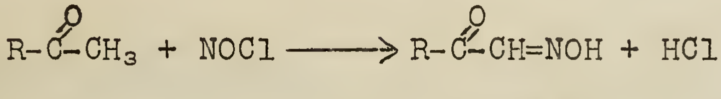
Secondary amines react with NOCl, in a manner previously mentioned in connection with monosubstituted amides, to give nitrosamines:



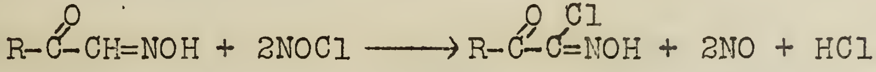
$$\mathrm{\begin{matrix}R\\R\end{matrix}\!>\!N{-}H \xrightarrow{NOCl} \begin{matrix}R\\R\end{matrix}\!>\!N{-}NO}$$

D. Ketones, aldehydes, ketoximes, and aldoximes

A large number of ketones have been treated with NOCl and react according to the following equations:

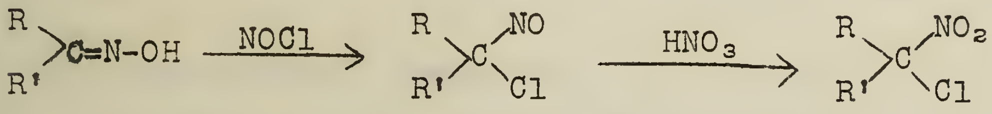
(1) 

$$R-\overset{O}{\overset{\|}{C}}-CH_3 + NOCl \longrightarrow R-\overset{O}{\overset{\|}{C}}-CH=NOH + HCl$$

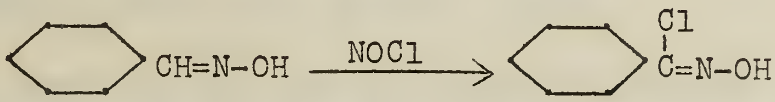
(2) 

$$R-\overset{O}{\overset{\|}{C}}-CH=NOH + 2NOCl \longrightarrow R-\overset{O}{\overset{\|}{C}}-\overset{Cl}{C}=NOH + 2NO + HCl$$

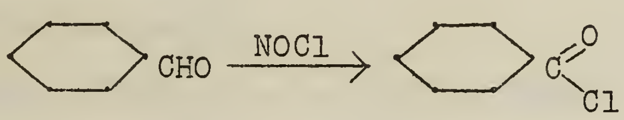
The reaction is controllable so that either product can predominate. When ketoximes (including cyclic ketoximes) are used as a starting material the chloronitroso derivative results; it is usually oxidized to the chloronitro derivative for identification:

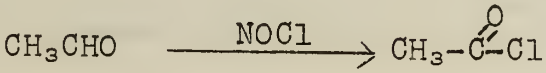


Aldoximes give the same type of reaction:



Aldehydes, themselves, are usually chlorinated to the acyl chloride, although the yields from aliphatic aldehydes are noticeably poor.

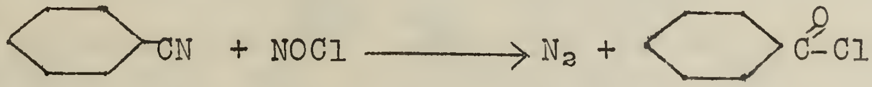


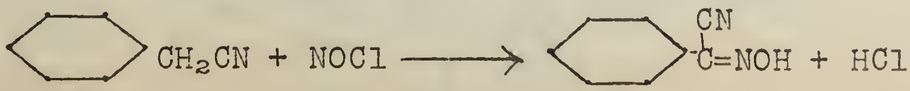


$$CH_3CHO \xrightarrow{NOCl} CH_3-\overset{O}{\overset{\|}{C}}-Cl$$

E. Nitriles

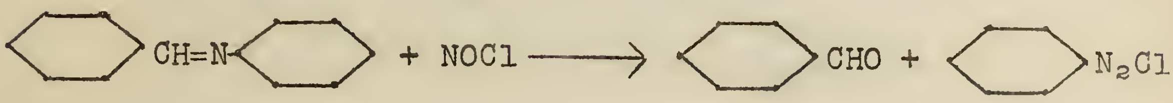
R. Perrot has recently used NOCl in treating nitriles to get the following results, finding that strictly aliphatic nitriles gave undesirable side-reactions:

(1) 

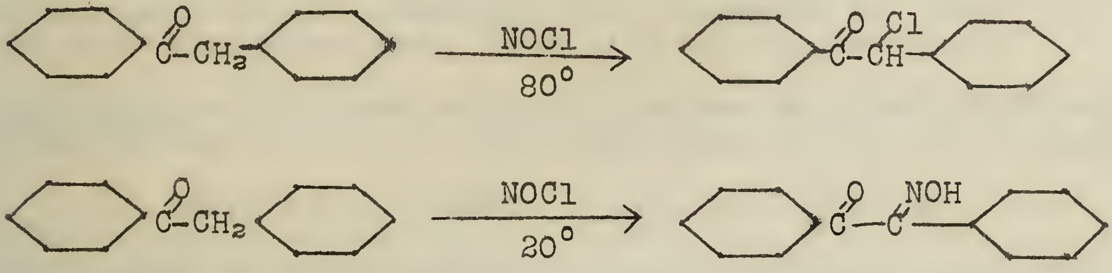
(2) 

F. Miscellaneous compounds

(1) Schiff bases:



(2) Desoxybenzoin:



(3) Organomercuri compounds:

(a) $R_2Hg + NOCl \longrightarrow RHgCl + RNO$

(b) $RHgX + NOCl \longrightarrow RNO + HgClX$

This last reaction has been used on polymethyl benzenes in transforming the mercuri-acetoxy group into a nitroso group, which can be reduced to an amino group. These amines and their derivatives can be used in identification of the original hydrocarbon.

(4) Grignard reagents:

$ArMgBr + NOCl \longrightarrow ArNO + MgBrCl$

This method is generally applicable for the preparation of aromatic nitroso compounds.

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Reported by J. J. Denton
December 21, 1938.

ORGANOMETALLIC COMPOUNDS OF THE ELEMENTS IN GROUP IIA

Charles Glacet --
H. Gilman -- Iowa State College
J. F. Durand -- University of Toulouse
E. Beckman -- University of Leipzig

The organometallic compounds of the metals in Group IIA have been rather extensively studied. Methods of preparation for compounds of the type RBeX, R_2Be, RCaI, and RBaI are to be found in the literature. Since organomagnesium compounds and their reactions have long been known, they will not be discussed.

Beryllium.--The first successful direct preparation of organoberyllium halides reported in the literature is that of Durand.

$$CH_3I + Be \xrightarrow{HgCl_2} CH_3BeI \qquad \text{(Durand)}$$

A second method is by the action of beryllium halide upon dialkyl beryllium.

$$R_2Be + BeX_2 \rightleftharpoons 2RBeX \qquad \text{(Gilman and Schulze)}$$

Gilman and Schulze investigated Durand's work and concluded that methylberyllium iodide could not be obtained directly by use of ordinary conditions. However, if the reaction were carried out in a sealed tube and kept at a temperature of 80-90° for fifteen hours, methylberyllium iodide could be obtained. The compounds they prepared in this way are:

$$CH_3BeI,\ C_2H_5BeI,\ C_2H_5BeBr,\ \underline{n}\text{-}C_4H_9BeI,\ C_6H_5BeI$$

In the case of phenylberyllium iodide a temperature of 150° must be used. Tertiary butyl chloride and tertiary butyl bromide appeared to react but the product gave no color with Michler's ketone. Other catalysts that may be used are beryllium chloride, a mixture of mercury and iodine, iodine, and bromine.

Methylberyllium iodide does not react with carbon dioxide but does react with phenylisocyanate to give acetanilide.

$$CH_3BeI + C_6H_5NCO \longrightarrow C_6H_5NHCOCH_3$$

Dialkyl beryllium may be prepared as follows:

$$BeCl_2 + 2RMgX \longrightarrow R_2Be + MgX_2 + MgCl_2 \qquad \text{(Krause and Wendt)}$$

$$Be + Me_2Hg \xrightarrow[130^\circ]{\text{sealed tube}} Me_2Be \qquad \text{(Lavroff)}$$

The first method given is much the better.

Beryllium dialkyls decompose rapidly in air and in the presence of carbon dioxide. They give an immediate color test with Michler's ketone. Some of the reactions given for these compounds are:

$$(CH_3)_2Be + CO_2 \longrightarrow CH_3CO_2H$$

$$(CH_3)_2Be + C_6H_5NCO \longrightarrow C_6H_5NHCOCH_3$$

$$(CH_3)_2Be + (C_6H_5)_2CO \longrightarrow (C_6H_5)_2COHCH_3$$

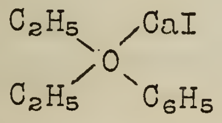
$$(C_2H_5)_2Be + (C_6H_5)_2CO \longrightarrow (C_6H_5)_2CHOH$$

$$(CH_3)_2Be + C_6H_5COCl \longrightarrow C_6H_5COH(CH_3)_2$$

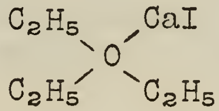
It is seen that dimethyl beryllium reacts with benzophenone in a normal manner, but diethyl beryllium results in reduction to diphenyl carbinol.

Dialkyl beryllium compounds are of the same order of reactivity as the corresponding Grignard reagents, while alkyl beryllium halides are much less reactive.

Calcium.--Beckmann found that calcium and phenyl iodide react, in the presence of a trace of iodine, to give an organocalcium iodide. During the reaction a brown powder separated, analysis of which indicated a monoetherate of phenyl calcium iodide. He obtained analogous results with ethyl iodide and assigned the formulas below to the products obtained:



I



II

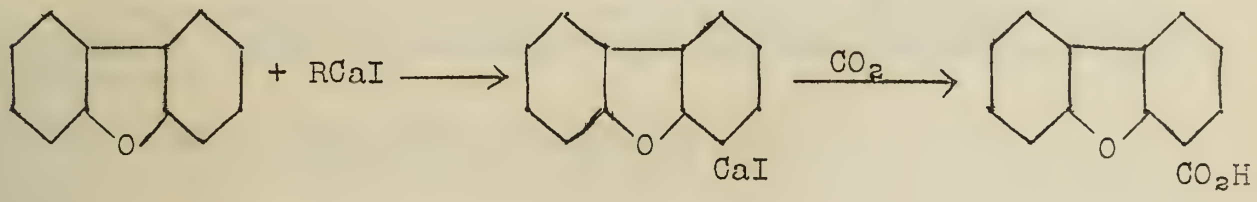
I and II reacted with carbon dioxide and subsequent hydrolysis produced benzoic and propionic acids respectively. They also reacted with benzaldehyde to give diphenyl carbinol and phenyl ethyl carbinol.

Gilman and Schulze repeated Beckmann's work and attempted to extend the reaction. They questioned the identity of the brown powder obtained by Beckmann and demonstrated that the organocalcium iodide was to be found in the ether solution. They also listed five objections to the use of these compounds in synthetic work.

1. The formation of RCaX appears to be restricted to iodides.
2. Only primary alkyl iodides undergo reaction with calcium.
3. The reaction is sluggish, irregular, and not always certain.
4. The yields are low. This is due in part to a coupling side reaction leading to R-R compounds.

5. Organocalcium iodides are less reactive than corresponding Grignard reagents.

The fifth statement was retracted later when they found that organocalcium iodides undergo metallation with dibenzofuran and add 1,2 to the double bond in benzophenone anil.



$$(C_6H_5)_2C{=}NC_6H_5 + C_6H_5CaI \longrightarrow (C_6H_5)_3CNHC_6H_5$$

Glacet showed the brown powder obtained by Beckmann to be a half and half mixture of I and the dietherate of calcium iodide. He used as a catalyst a small amount of Grignard reagent or of the organocalcium compound. The methods of preparation used were the same as that for Grignard reagents, except that in some cases the pressure on the system was increased and the size and type of calcium shavings were specified. Glacet was able to obtain a reaction with secondary as well as primary iodides, but he was not able to obtain a reaction with bromides and chlorides. The organocalcium compounds reacted normally with aldehydes, ketones, and esters to give carbinols, and with nitrites to give ketones. Acid chlorides would not react.

The compounds which he reported are given below.

Reactive:

CH_3I, C_2H_5I, $CH_3CH_2CH_2I$, $CH_3(CH_2)_2CH_2I$, $CH_2{=}CHCH_2I$,

$(CH_3)_2CHCH_2CH_2I$, $CH_3(CH_2)_6CH_2I$, C_6H_5I, $\underline{m}$-$CH_3C_6H_4I$

Difficultly reactive:

$CH_3CHIC_2H_5$, CH_3CHICH_3

Unreactive:

$CH_3CH_2CI(CH_3)_2$, $(CH_3)_3CI$

Strontium.--Very little mention is made in the literature of organostrontium compounds except to predict them more reactive than the calcium compounds and less reactive than barium compounds.

Barium.--Gilman and Schulze have reported the preparation of phenyl barium iodide by the use of electrolytic barium and pure phenyl iodide. They have also prepared ethylbarium iodide under similar conditions. The catalyst used was a trace of iodide.

The reactions studied were those with carbon dioxide, β-naphthyl isocyanate, and ethyl benzoate.

Apparently the order of reactivity of the organometallic compounds of Group IIA increases with increase in atomic weight of the metal.

$$RBeX < RMgX < RCaX < RSrX < RBaX$$

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Reported by Wm. H. Sharkey
December 21, 1938

THE DIELS-ALDER REACTION IN THE SYNTHESIS OF CYCLIC COMPOUNDS

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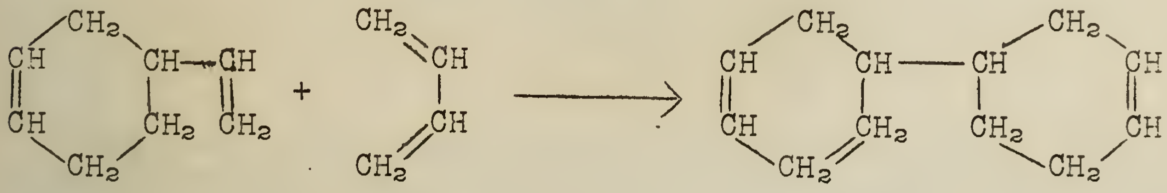
Erwin Windmuth -- Universität of Köln am Rhine

Recently Alder and Rickert reported the preparation and the structure of a trimeric butadiene. The hydrocarbon having the structure of △-3,3'-octahydrobiphenyl (II) is produced by a 1,4-addition of butadiene to the vinyl group of dimeric butadiene.

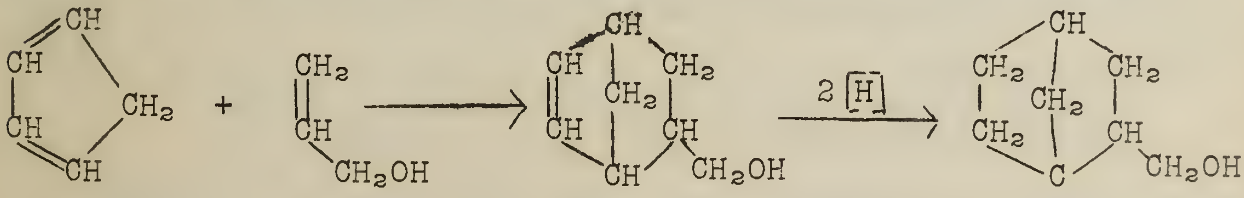


II

The fundamentals of this newer method had been pointed out previously in other investigations. Here we can see that for the first time a double bond, $RCH=CH_2$ which does not belong to the type C=C-C=O, C=C-C=C or C=C-C≡N and is assumed to be devoid of any special structure, has the capability of undergoing the diene synthesis. The discovery has stimulated the investigation of a series of simple and now, through the use of this property, easily obtainable olefinic compounds.

I. Diene Synthesis with Allyl Alcohol and its Derivatives.-- To place the investigation on a firm foundation it seemed advisable to begin the work with allyl alcohol and cyclopentadiene. It was shown that when equal molal quantities of both components were heated together in a sealed tube at 175-180° a 60-70 per cent yield was obtained. This was general for most of the reactions carried out.

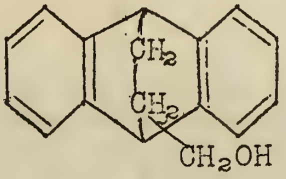
The addition product (III) takes up 2 atoms of hydrogen upon catalytic hydrogenation and is converted to the saturated alcohol (IV), which had been prepared previously by catalytic reduction of the acrolein addition product.



III IV

It was further shown that the reactivity of allyl alcohol was not altered by causing such of its esters as the salicylate and the diphthalate to undergo the condensation also. The reaction was shown to be the same by hydrogenation and subsequent hydrolysis to the free saturated alcohol (IV).

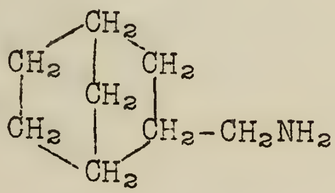
In order to show that this reaction was not specific for the cyclopentadiene, similar condensations were run on anthracene in benzene solution at 210-220°. This reaction likewise proceeded in a smooth manner to yield the new alcohol (V), by adding across the center ring.



V

Similarly other homologs and derivatives of allyl alcohol were caused to undergo this condensation and every case the reactions proceeded smoothly although some went more rapidly than others. Among the compounds used were the allyl halides (and were shown to add in the conventional manner by conversion to the saturated alcohol by boiling the hydrogenated adduct with alkali), allyl amine, crotyl alcohol, vinyl acetic acid, allyl cyanide, allyl isothiocyanate and eugenol.

The allyl amine addition compound was of especial interest. Catalytic hydrogenation gave the saturated 3,6-endomethylene hexahydrobenzylamine (VI).



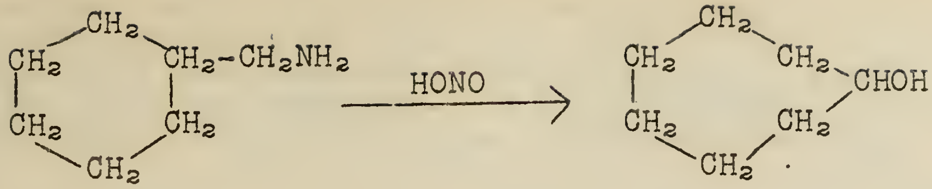
VI

The structure of the diene condensation was shown to be the same as that of the alcohol of halide condensates by obtaining the amine in two other ways:

a) By the Grabriele methods, from the allyl bromide-cyclopentadiene adduct and potassium phthalimide.

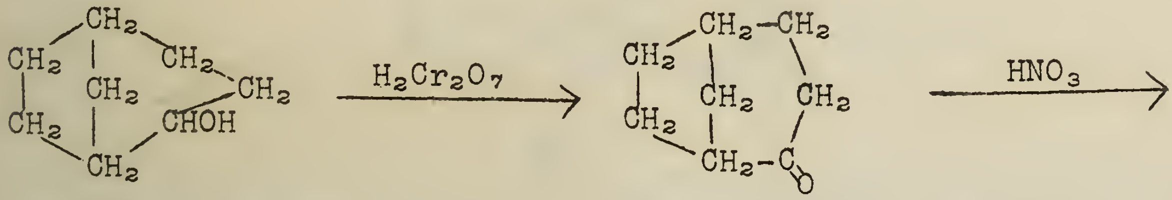
b) By the action of Mg and CO_2 on the allyl halide adduct to the corresponding acid, which in turn was degraded to the amine by the Curtius method.

Similarly it was thought that the hydrogenated alcohol could be obtained by the action of nitrous acid on the hydrogenated amine. An alcohol was obtained but was found not to be isomeric with any of the diastereoisomers of the original 2,5-endomethylene hexahydrobenzyl alcohol. An investigation of the literature showed that such a change was not particularly astounding. Demjanow, Ruzicka and other workers have reported similar cases such as the conversion of cyclohexylmethyl amine to cycloheptanol (VII)

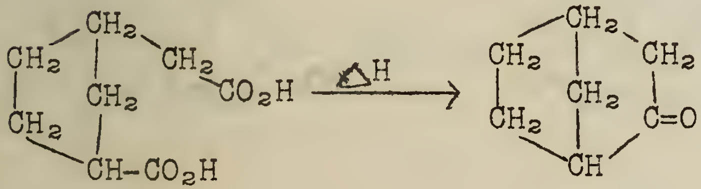


VII

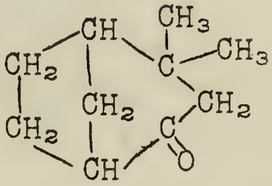
That a similar ring change had taken place on this occasion was shown in the following manner: The new alcohol (VIII) gives on chromic acid oxidation the ketone (IX) which was compared to a similar known compound (X). Nitric acid oxidation of IX gave a dicarboxylic acid (XI), which by distillation of its lead salt yields norcamphor (XII).



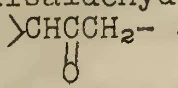
VIII IX



XI XII



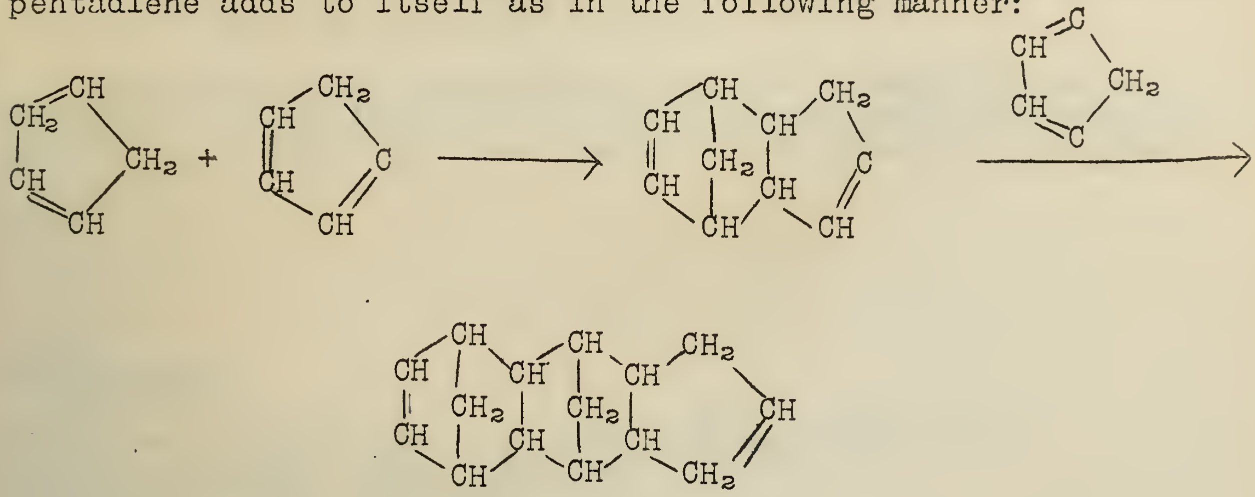
X

The last step in the conversion of XI to XII is already described in the literature and both are known compounds. However, the foregoing does not completely clinch the positions of the CHOH or CO groups in VIII or IX. From the mode of origin of the alcohol, these groups could exist in either the 2- or 3-position of the ring system. To clinch the matter the ketone (IX) was condensed with an excess of anisaldehyde and a monoanisole compound was obtained. This indicated a  $\rangle\mathrm{CH}\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{CH_2}-$ arrangement and fixes the carbonyl group in position 2.

A carbonyl in position 3 would be flanked by two methylene groups and would give a dianisole derivative.

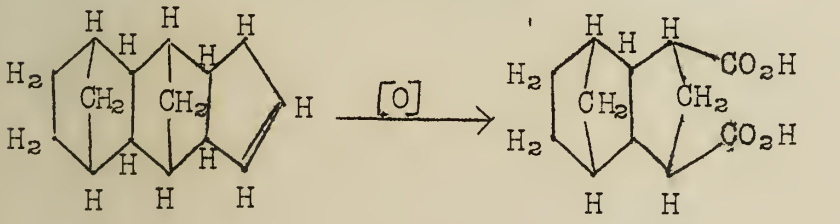
II. The 1,4,5,8-bis-Endomethylene decalins.--Through the introduction of the diene synthesis the work on the terpene series has been stimulated. It offers a method of introducing bridges into ring compounds to form combinations which were formerly difficult to produce. These are important not only to complete the synthesis of the compounds in the hydro-aromatic system but also because a knowledge of the relationships between ring structure and the physical characteristics are of interest.

The authors were successful in preparing derivatives of 1,4,5,8-bis-endomethylene decalin (XIII). The work of Alder and Stein on the polymerization of the cyclopentadienes indicated a possible mode of formation of these compounds. It had been shown that cyclopentadiene adds to itself as in the following manner:

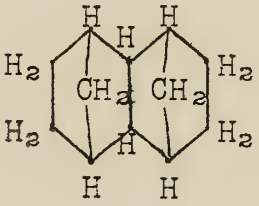


XIV

Partial hydrogenation of XIV yielded XV which upon thorough oxidation was converted to the dicarboxylic acid (XVI).

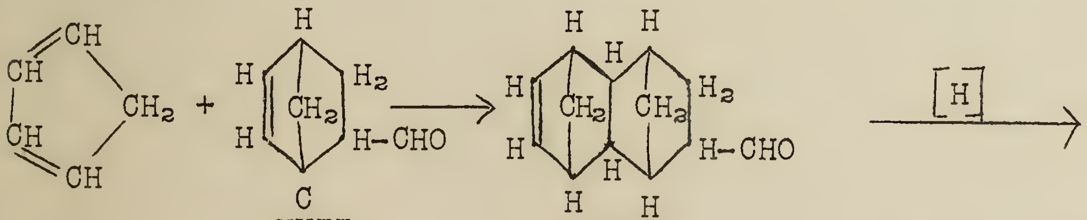


XV XVI

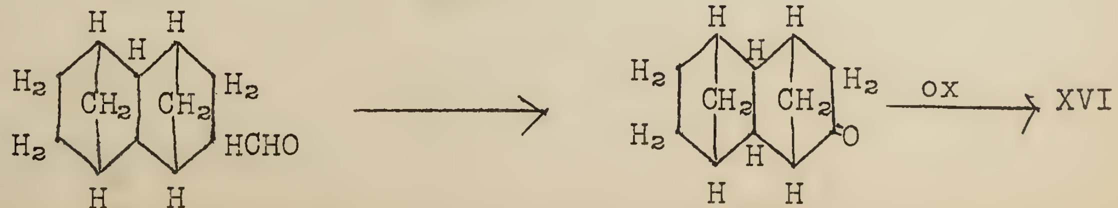


XIII

In a corresponding manner the product of diene addition of one mole of cyclopentadiene and acrolein (XVII) added another molecule of cyclopentadiene at 170-180° to give XVIII. This was hydrogenated to give XIX and then degraded through its enol acetate to the ketone XX. The ketone upon nitric acid oxidation yielded the

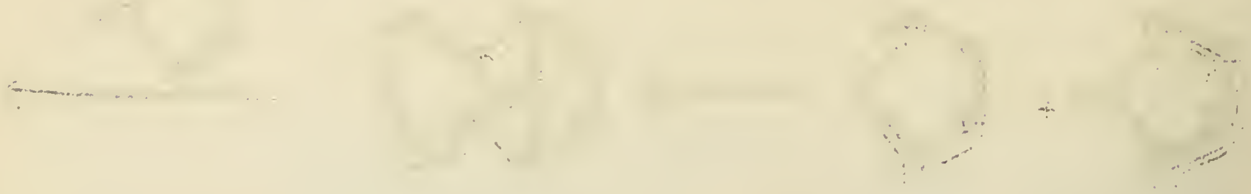


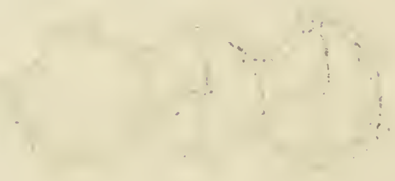
XVII XVIII



XIX XX

[illegible]





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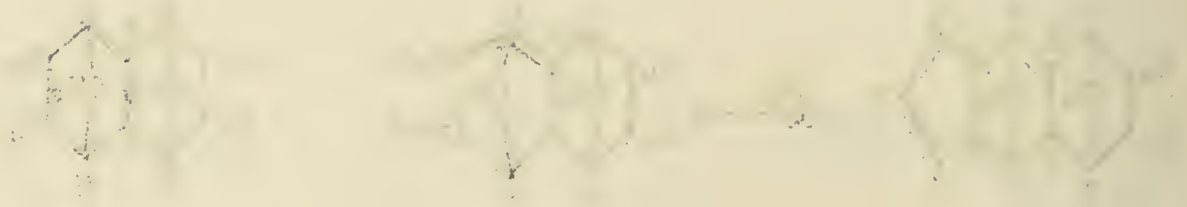

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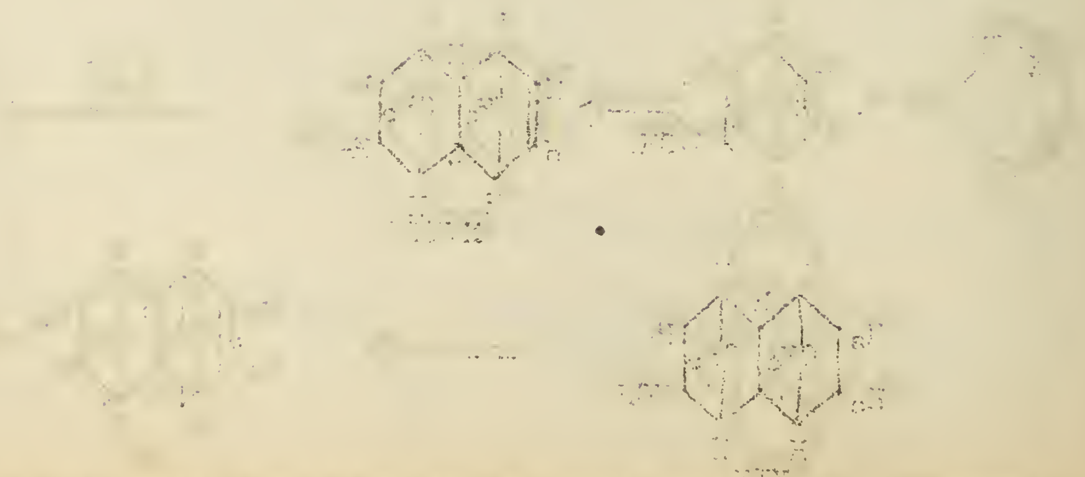

dicarboxylic acid (XVI) and thereby clinched its structure. Further, by the method of Wolff-Kishner the semicarbazone of XX was easily reduced to the stem hydrocarbon (XIII).

Similarly, other derivatives can also be made for, as was described in an earlier part of this paper, various allyl compounds can be made to undergo this condensation at elevated temperatures.

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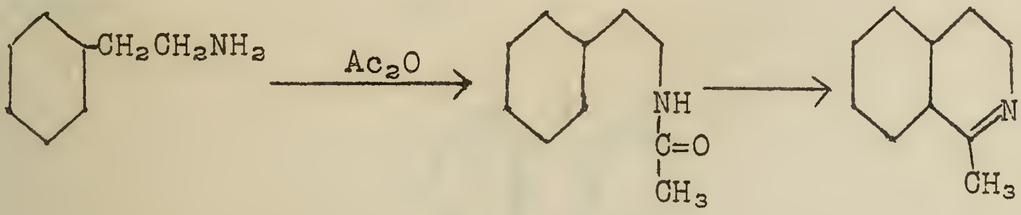
Reported by Marvin H. Gold
January 11, 1939

SOME CONDENSATION REACTIONS OF TRYPTAMINE

Hahn, Hansel, Gudjons -- Universität Frankfurt a. M.

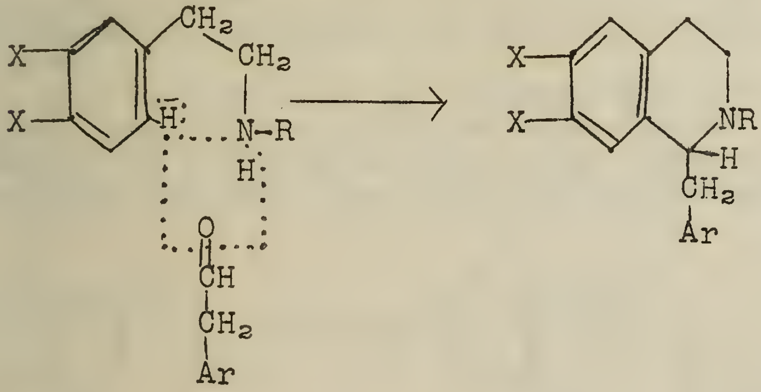
In 1893 Bischler and Napieralsky tried to synthesize isoquinolines by treating β-phenylethylamine with acetic anhydride and closing the ring by dehydrating with P_2O_5:



$CH_2CH_2NH_2$
Ac_2O
NH
C=O
CH_3
N
CH_3

However, their yields were not very satisfactory.

Winterstein in 1910 suggested this mechanism for the rise of alkaloids in plants:

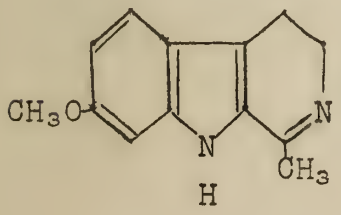


X
X
CH_2
CH_2
H
N-R
H
O
CH
CH_2
Ar
X
X
NR
H
CH_2
Ar

R = H or $-CH_3$

This method involves the condensation of the amine with an aldehyde and then loss of water to close the ring.

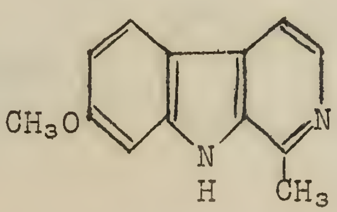
Späth and Lederer used the former type to synthesize compounds in the hormane-type alkaloid group.



CH_3O
N
H
N
CH_3

I

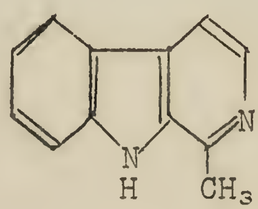
harmaline



CH_3O
N
H
N
CH_3

II

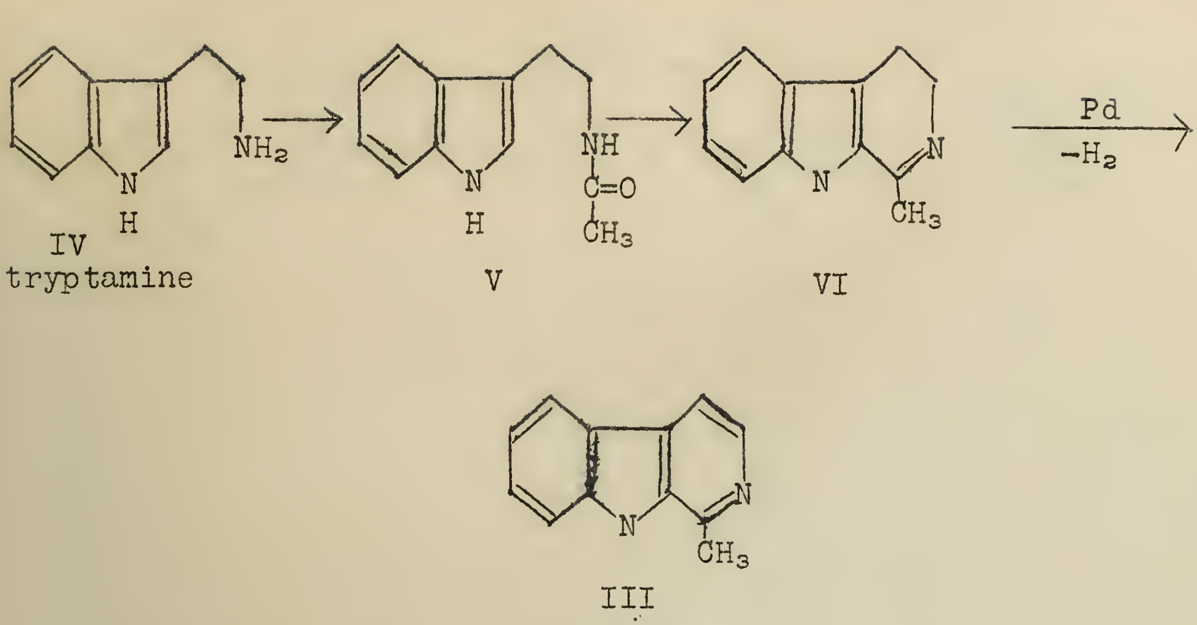
harmine



III

harmane

The preparation of harmane may be used as an example:


NH$_2$
NH
C=O
CH$_3$
N
H
CH$_3$
Pd
-H$_2$

IV
tryptamine

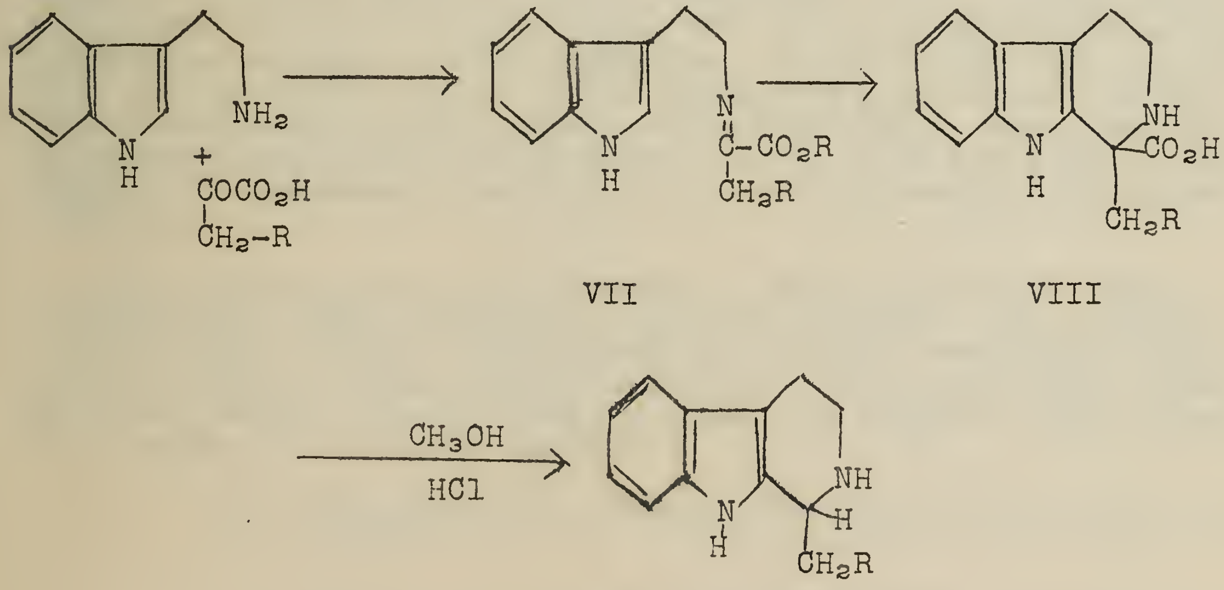
V

VI

III

The dihydroharmane (VI) was obtained in 56 per cent yield and the dehydrogenation resulted in 89 per cent yield of III.

The mechanism of the condensation of tryptamine with α-keto acids, however, had not been investigated. Hahn chose pyruvic acid because all previous α-keto acids, except pyruvic, on boiling with alcoholic HCl lost CO_2 after the condensations took place.

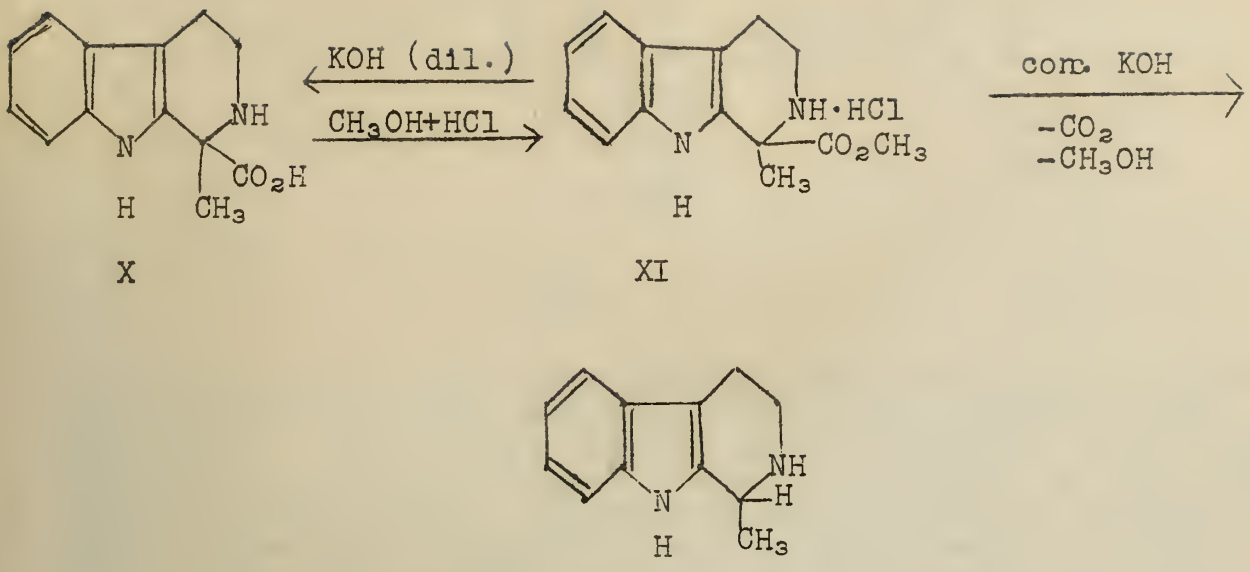

NH$_2$
N
H
+
COCO$_2$H
CH$_2$-R
N
C-CO$_2$R
CH$_2$R
NH
CO$_2$H
CH$_2$R
CH$_3$OH
HCl
NH
H
CH$_2$R

VII

VIII

IX
except where R=H

With pyruvic acid the ester hydrochloride (XI) was formed under milder conditions.



XII
tetrahydroharmane

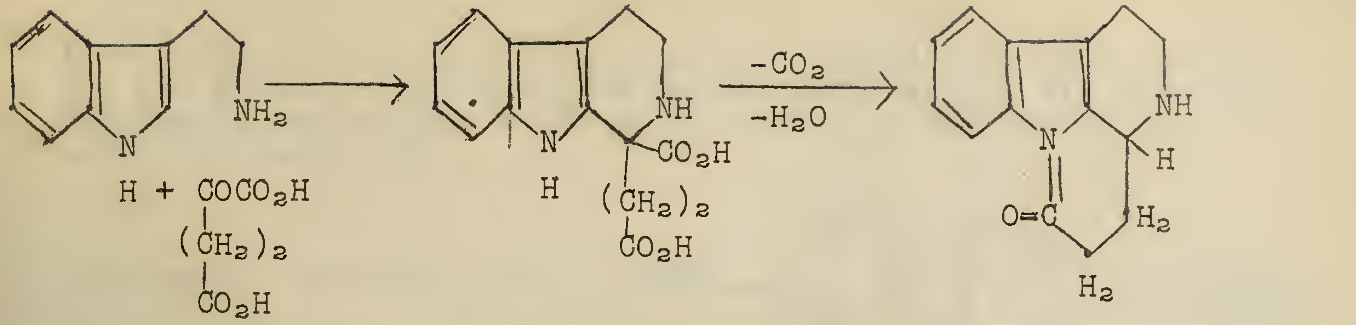
Strong alkali yielded the known compound (XII) but careful hydrolysis yielded some of the starting material (X) as well as XII. In this manner he showed that when the acid was condensed, the carboxyl was not involved in the ring closure.

Hahn had tried previously these condensations in the isoquinoline series and found that the reaction was not smooth unless carried out under physiological conditions, i.e., in the presence of acetate or phosphate buffers. The same principle applied to tryptamine except, to their surprise, at pH 1. Here the condensation went smoothly and in yields averaging greater than 50 per cent. Some phenyl substituted pyruvic acids were used. For example, *m*-hydroxy phenylpyruvic acid gave a yield of 41 per cent of the expected 3-(*m*-hydroxybenzyl)-3,4,5,6-tetrahydrocarboline hydrochloride.

The reaction was next extended to α-keto glutaric acid, prepared from ethyl succinate and ethyl oxalate. The reaction followed the expected course until the product was heated with alcoholic HCl to cause decarboxylation. Here a molecule of water was lost, as well as CO$_2$, and an amide was formed. Hahn assigns it the formula XIV for two reasons:

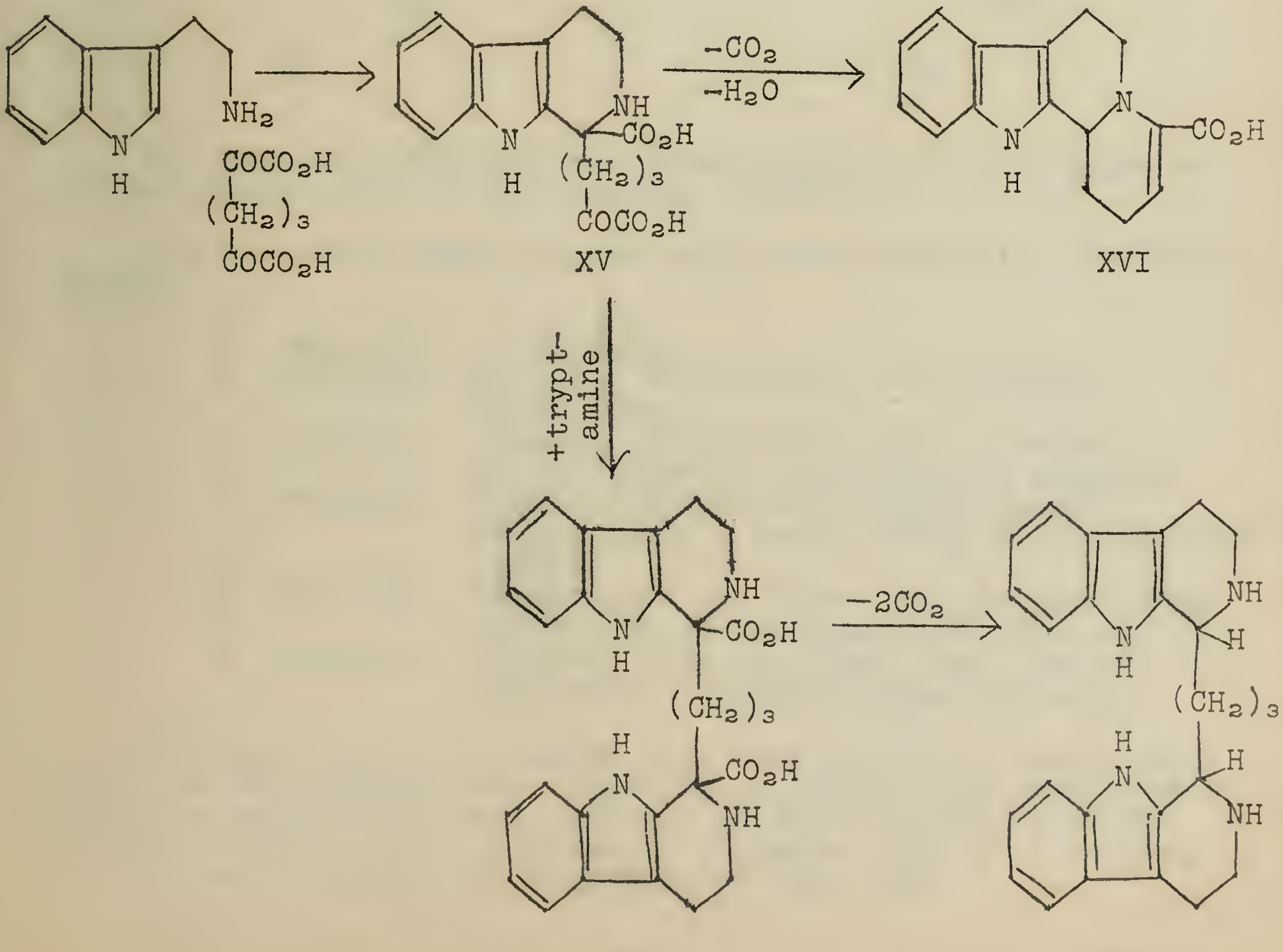
1. A six-membered is usually formed in preference to a five.

2. All attempts to make hydrochlorides of carbazole derivatives (containing no other N) are not successful because the carbazole and pyrrole nitrogen has no basic properties. Since Hahn's compound forms a stable hydrochloride, it must have formula XIV.


NH2
H + COCO2H
(CH2)2
CO2H
NH
CO2H
H
(CH2)2
CO2H
-CO2
-H2O
NH
N
H
O=C
H2
H2

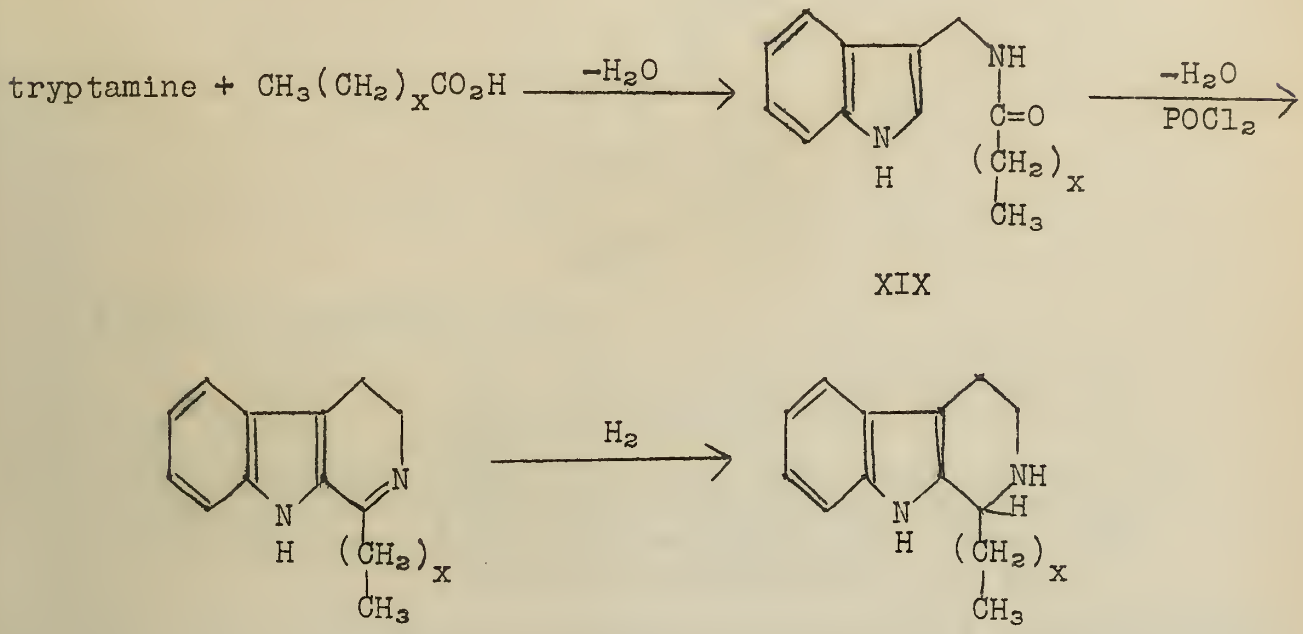
XIII XIV

With two molecules of tryptamine and one molecule of α,α'-diketo pimelic acid the reaction follows the expected course, XV ⟶ XVIII. These diketo dibasic acids are hard to obtain and the above mentioned acid was the only one obtained by the authors. An interesting reaction occurred if only one mole of tryptamine was used. After the condensation the ring was closed by losing a molecule of water from the NH and the enol of the second carbonyl. This is illustrated in the step XV ⟶ XVI. Synthesis of alkaloid derivatives by α,α'-diketo dibasic acids is limited by the difficulty in obtaining these acids.


N
H
NH2
COCO2H
(CH2)3
COCO2H
NH
CO2H
(CH2)3
COCO2H
XV
-CO2
-H2O
N
CO2H
XVI
+trypt-
amine
NH
CO2H
(CH2)3
CO2H
NH
-2CO2
NH
H
(CH2)3
H
NH

XVII XVIII

Hahn and Gudjons wished to extend this synthesis so they adopted the old method of Bischler and Napieralsky using a 2:1 ratio of tryptamine and dibasic acids or 1:1 ratio of tryptamine and a monobasic fatty acid.



XIX

XX

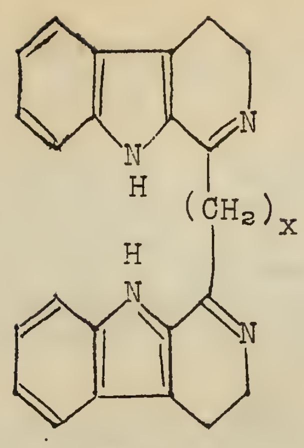
XXI

The condensations with the dibasic acids should follow the general course and produce homologs of XVIII.

The following dibasic acids were tried giving the yields as listed:

1. Malonic: no diamide.
2. Succinic: diamide, 64 per cent; ring closure, 0 per cent.
3. Adipic: diamide, 70 per cent; ring closure, 99 per cent; no hydrogenation product.
4. Pimelic: diamide, 56 per cent; ring closure, 94 per cent; a small amount of hydrogenation product.
5. Suberic: diamide, 64 per cent; ring closure, yield not given; no hydrogenation product.
6. Sebacic: diamide, 86.5 per cent; ring closure, 99 per cent; no hydrogenation product.

Although the ring closures went very smoothly, the product could not be hydrogenated. First Na in alcohol was tried but no reduction took place, then hydrogen in the presence of Adams' catalyst yielded only a mixture of products. So the syntheses in this series ended with compounds of type XXII.



XXII

Aliphatic monobasic acids.

1. Valeric: amide, 65 per cent; ring closure, 91 per cent; hydrogenation, 100 per cent yield.
2. Palmitic: amide, 96.5 per cent; ring closure, 98 per cent; hydrogenation, 100 per cent.
3. Stearic: Amide, 75 per cent; ring closure, 80 per cent; hydrogenation, not given.

In 1 and 2 the reduction was carried out with Adams' catalyst adding one mole of hydrogen. In 3 a good reduction was obtained by the use of sodium and alcohol.

Hahn and Gudjons make no comment on the contrast between these two series with respect to ease of hydrogenation.

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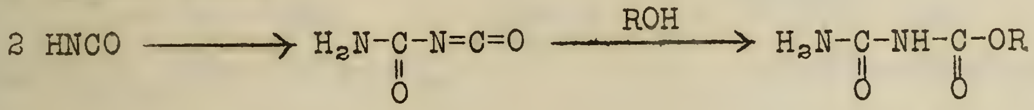
Reported by J. H. McCracken
January 11, 1939.

THE STRUCTURE OF α-TOCOPHEROL (VITAMIN E)

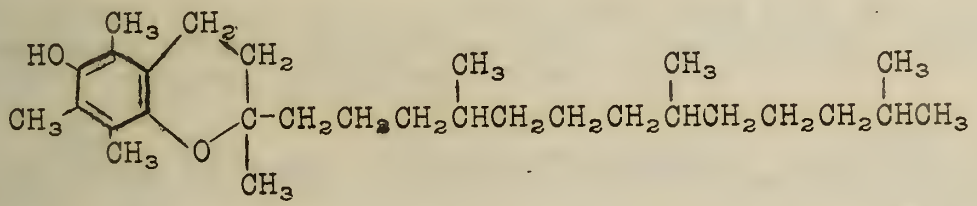
Karrer - University of Zurich
Fernholz - Merck and Co., Rahway, N.J.

The unsaponifiable fraction of wheat germ, cottonseed, and palm oils contains several substances which show Vitamin E (antisterility) activity. The most effective of these substances has been designated α-Tocopherol. It may be separated from the less active β- and γ-Tocopherols by chromatographic adsorption and/or recrystallization and subsequent hydrolysis of its allophanate formed by reaction with cyanic acid:



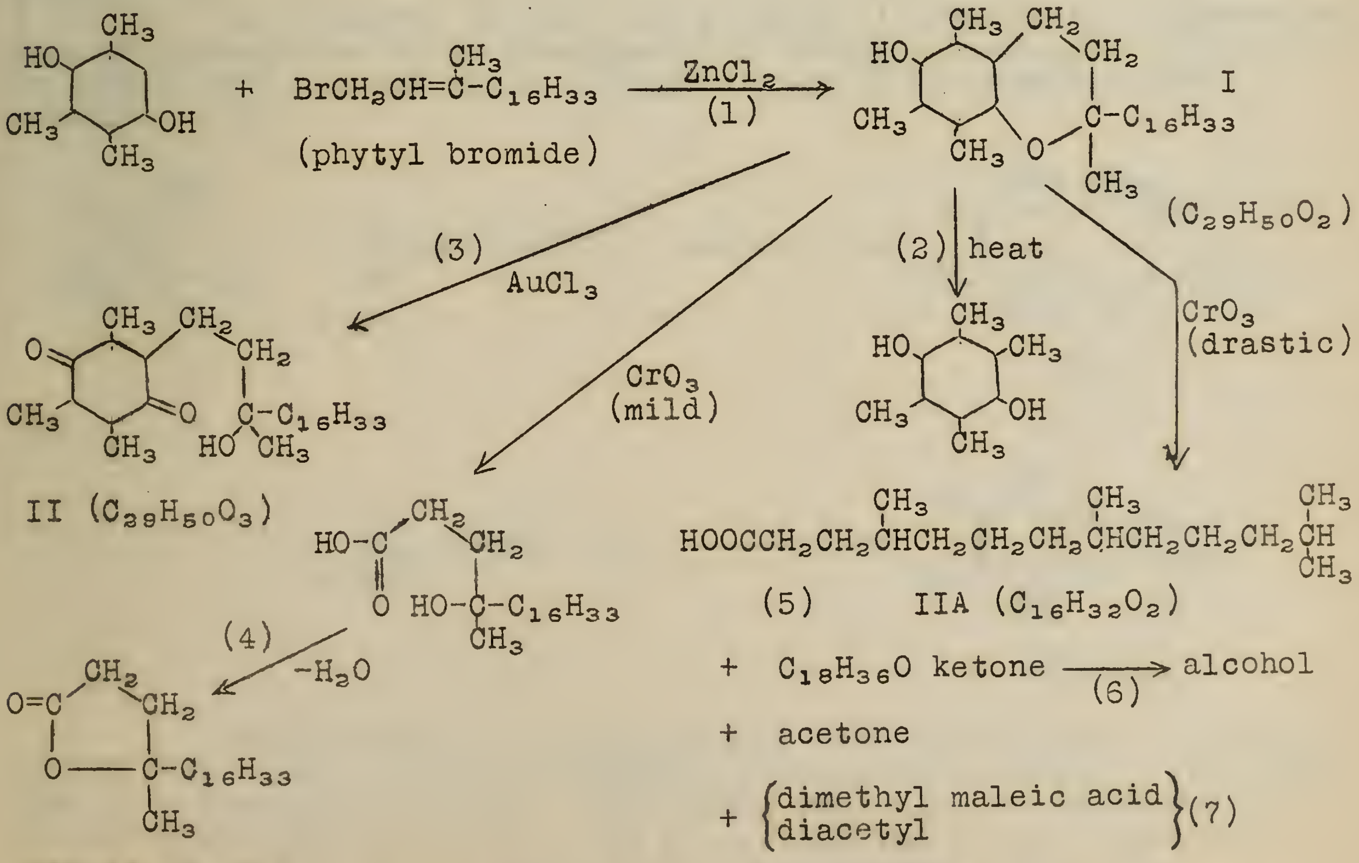
$$2\ \mathrm{HNCO} \longrightarrow \mathrm{H_2N{-}\underset{\underset{O}{\|}}{C}{-}N{=}C{=}O} \xrightarrow{\mathrm{ROH}} \mathrm{H_2N{-}\underset{\underset{O}{\|}}{C}{-}NH{-}\underset{\underset{O}{\|}}{C}{-}OR}$$

Karrer and Fernholz independently have deduced the same structure for α-Tocopherol:



I

The most important reactions involved in the proof of this structure were as follows:



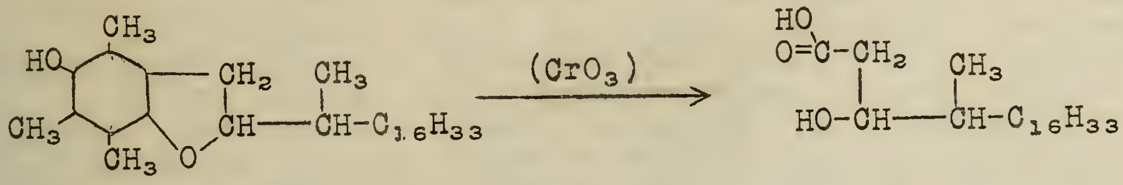
+
BrCH₂CH=C(CH₃)-C₁₆H₃₃
(phytyl bromide)
ZnCl₂
(1)
I
(C₂₉H₅₀O₂)
(3)
AuCl₃
CrO₃
(mild)
(2) heat
CrO₃
(drastic)
II (C₂₉H₅₀O₃)
(4)
-H₂O
III (C₂₁H₄₀O₃)
(5)
IIA (C₁₆H₃₂O₂)
+ C₁₈H₃₆O ketone → alcohol
(6)
+ acetone
+ dimethyl maleic acid, diacetyl
(7)

The numbers in parentheses refer to notes on the pages which follow.

Notes:

(1) The natural α-Tocopherol is optically active. Resolution of the synthetic product with 3-bromo-d-camphorsulfonyl chloride gave a compound identical in every respect with the natural product. That a chromane (I) and not a cumarane (IV) compound is formed is indicated by the following facts:

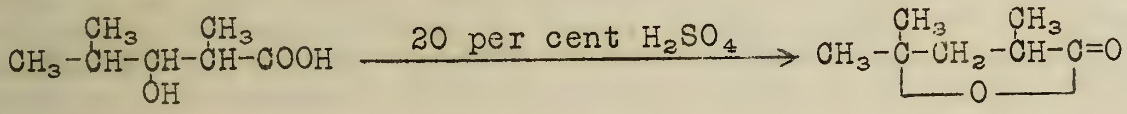
(a) Fernholz showed that a lactone (III) was formed by reaction (4) (mild oxidation) as predicted by a chromane structure. A cumarane ring such as (IV) would have given a β-hydroxy acid:



CH3
HO
CH3
CH3
O
CH2
CH3
CH
CH-C16H33
(CrO3)
HO
O=C-CH2
CH3
HO-CH
CH-C16H33

(IV)

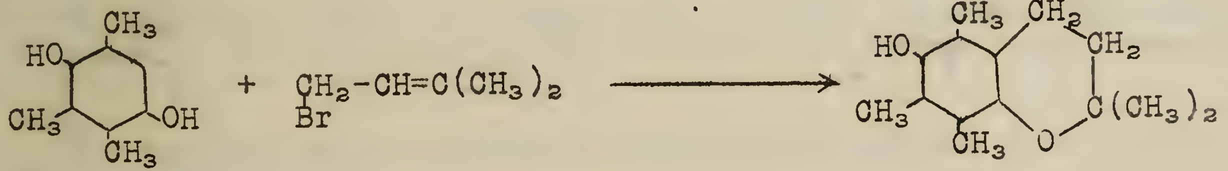
Karrer suggested that the lactone might have been the result of a rearrangement of the β-hydroxy acid. Pospjechoff, Raichstein and Braun have reported reactions of this type:



$$CH_3-\overset{CH_3}{CH}-\underset{OH}{CH}-\overset{CH_3}{CH}-COOH \xrightarrow{\text{20 per cent } H_2SO_4} CH_3-\underbrace{\overset{CH_3}{C}-CH_2-\overset{CH_3}{CH}-C}_{O}=O$$

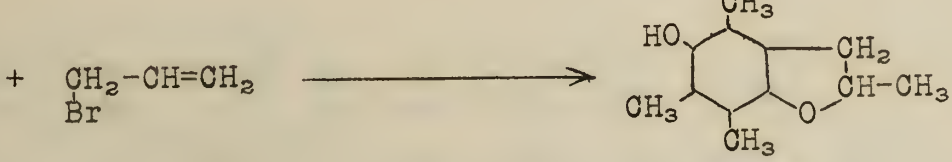
Emerson, however, obtained Fernholz's lactone by a neutral $KMnO_4$ oxidation.

(b) Claisen, Karrer, and L. Smith independently demonstrated that γ-substituted allyl bromides give chromane compounds (V) on condensation with phenols while unsubstituted allyl bromides give cumaranes (VI):



CH3
HO
CH3
OH
CH3
+
CH2-CH=C(CH3)2
Br
CH3
CH2
HO
CH2
CH3
C(CH3)2
CH3
O

(V)

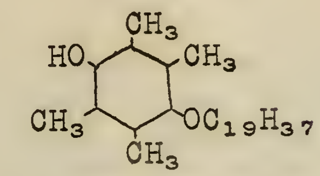


+
CH2-CH=CH2
Br
CH3
HO
CH2
CH-CH3
CH3
O
CH3

(VI)

(c) Oxidation of α-Tocopherol with $AuCl_3$ gives a tertiary alcohol (II). By a similar oxidation the cumarane formula (IV) would lead to a secondary alcohol. This $AuCl_3$ oxidation is quantitative and has been applied by Karrer to the estimation of the Vitamin E content of various oils. The β- and γ-Tocopherols and the carotenoids interfere.

(2) The formation of durohydroquinone by thermal decomposition led John to suggest a simple ether formula:



The evidence against such a structure includes the following facts:

(a) The butyl, cetyl, and dodecyl ethers have in common an absorption spectra which is different from that of α-Tocopherol.

(b) The ethers reduce $AgNO_3$ much more slowly and give duroquinone. α-Tocopherol gives a compound with practically no change in molecular weight. This is evidence for a carbon-carbon as well as a carbon-oxygen link between the two parts of the molecule.

(c) The common ether splitting reagents do not yield durohydroquinone from α-Tocopherol.

(3) See note (1-c).

(4) See also note (1-a). The lactone III was oxidized only by degradation. Esterification by CH_3OH (H_2SO_4) could not be accomplished. These facts lend further support to the chromane ring structure by indicating the formation of a tertiary and not a secondary alcohol.

(5) Degradation of the $C_{16}H_{32}O_2$ acid gave two full moles of acetic acid. Since this determination is never quantitative with saturated compounds, it was assumed that at least three methyls were present. Acetone was found, though in small amounts. Its presence indicates the existence of an isopropyl group. The isoprene rule was applied in the derivation of the formula (IIA) for the acid.

(6) The $C_{18}H_{36}O$ ketone was found only in small amounts. It was not isolated but was converted to the alcohol from which a dinitrobenzoate was prepared.

(7) The dimethyl maleic acid and the diacetyl result from degradation of the aromatic ring.

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Reported by S. C. Kelton
January 18, 1939

SELENIUM DIOXIDE AS AN OXIDIZING AGENT IN ORGANIC CHEMISTRY

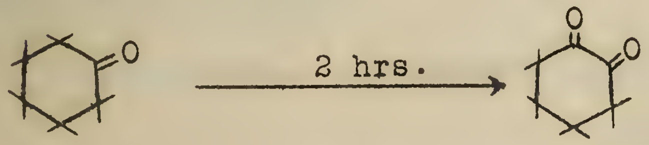
K. Kratzl - University of Wien

The oxidation processes have always been of great importance in organic chemistry both in the synthesis of new compounds and in determining constitution. Selenium dioxide was slow in finding application as an oxidizing agent in organic chemistry until 1932-34 when H. L. Riley published his work as summarized below:

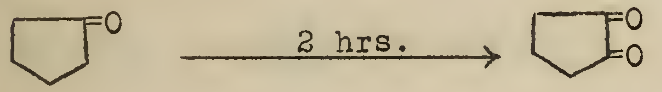
I. Carbonyl Compounds

1. $CH_3COCH_3 \xrightarrow{\text{4 hrs.}} CH_3COCHO$ 60 per cent
2. $CH_3CH_2CHO \xrightarrow{\text{4 hrs.}} CH_3COCHO$ 30 per cent
3. $CH_3CH_2COCH_3 \xrightarrow{\text{4 hrs.}} CH_3CH_2COCHO + CH_3COCOCH_3$

   22 per cent
4. $CH_3CH_2CH_2CHO \xrightarrow{\text{4 hrs.}} CH_3CH_2COCHO$ 45 per cent
5. $CH_3CH_2COCH_2CH_3 \xrightarrow{\text{4 hrs.}} CH_3COCOCH_2CH_3$ (not isolated)
6. $CH_3CHO \xrightarrow[\text{2 hrs.}]{\text{autoclave}} CHOCHO$ 90 per cent
7. $C_6H_5COCH_3 \xrightarrow{\text{2 hrs.}} C_6H_5COCHO$ 50 per cent
8. $C_6H_5CH_2CHO \xrightarrow{\text{2 hrs.}} C_6H_5COCHO$ 35 per cent
9. $C_6H_5COCH_2CH_3 \xrightarrow{\text{12 hrs.}} C_6H_5COCOCH_3$ 50 per cent

10.


35 per cent

11.


7 per cent

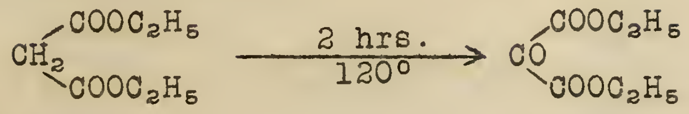
Selenium dioxide has a specific action on aldehydes and ketones of various types whereby 1,2-diketones and aldoketones are conveniently obtained in quantity. Ketones which contain no methylene group, i.e. benzophenone, are oxidized by selenium dioxide only upon strong heating and complete oxidation occurs. Compounds which contain a methylene group activated by proximity to a negative group appear to be specifically oxidized at reasonably low temperatures.

II. Alcohols and Esters

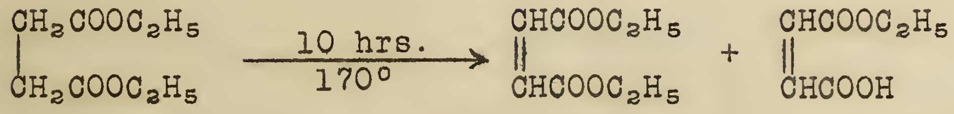
Levulose is the only common sugar which reduces selenium dioxide.

12. $C_2H_5OH \xrightarrow[200^\circ]{\text{autoclave}} CHOCHO$ 41 per cent

13. $C_6H_5CH_2OH \xrightarrow{10\ hrs.} C_6H_5CHO$ 45 per cent

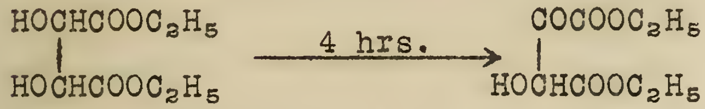
14. 

$CH_2\begin{array}{l}COOC_2H_5\\COOC_2H_5\end{array} \xrightarrow[120^\circ]{2\ hrs.} CO\begin{array}{l}COOC_2H_5\\COOC_2H_5\end{array}$ 32 per cent

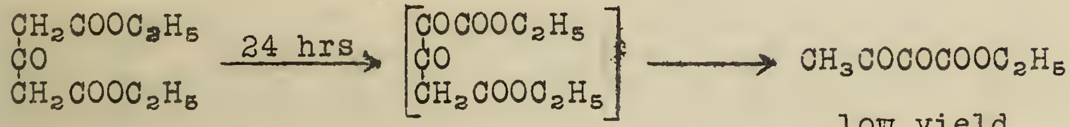
15. 

$\begin{array}{l}CH_2COOC_2H_5\\|\\CH_2COOC_2H_5\end{array} \xrightarrow[170^\circ]{10\ hrs.} \begin{array}{l}CHCOOC_2H_5\\||\\CHCOOC_2H_5\end{array} + \begin{array}{l}CHCOOC_2H_5\\||\\CHCOOH\end{array}$

11 per cent 29 per cent

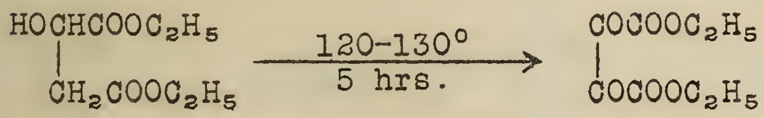
16. 

$\begin{array}{l}HOCHCOOC_2H_5\\|\\HOCHCOOC_2H_5\end{array} \xrightarrow{4\ hrs.} \begin{array}{l}COCOOC_2H_5\\|\\HOCHCOOC_2H_5\end{array}$ 38 per cent

17. 

$\begin{array}{l}CH_2COOC_3H_5\\CO\\CH_2COOC_2H_5\end{array} \xrightarrow{24\ hrs.} \left[\begin{array}{l}COCOOC_2H_5\\CO\\CH_2COOC_2H_5\end{array}\right] \longrightarrow CH_3COCOCOOC_2H_5$

low yield

18. 

$\begin{array}{l}HOCHCOOC_2H_5\\|\\CH_2COOC_2H_5\end{array} \xrightarrow[5\ hrs.]{120-130^\circ} \begin{array}{l}COCOOC_2H_5\\|\\COCOOC_2H_5\end{array}$ 72 per cent

19. $C_6H_5CH_2CH_2COOC_2H_5 \xrightarrow[5\ hrs.]{200^\circ} C_6H_5CH{=}CHCOOH$ 8 per cent

20. $C_6H_5CHOHCOOC_2H_5 \xrightarrow[2.5\ hrs.]{} C_6H_5COCOOC_2H_5$ 60 per cent

21. $C_6H_5CH_2COOC_2H_5 \xrightarrow[2.5\ hrs.]{} C_6H_5COCOOC_2H_5$ 34 per cent

III. Unsaturated Compounds

22. $C_6H_5CH_2CH_2C_6H_5 \longrightarrow C_6H_5CH{=}CHC_6H_5 + C_6H_5COCOC_6H_5$

7 per cent 33 per cent

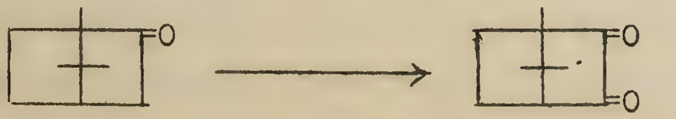
23. $CH_2{=}CH_2 \xrightarrow[250^\circ]{120^\circ} (CHOCHO)_3$ 33-84 per cent

$CH_2{=}CH_2 \xrightarrow{P_2O_5}$ small yield of monomer

24. $CH_3CH{=}CH_2 \xrightarrow{150^\circ} CH_3COCHO$ 19 per cent

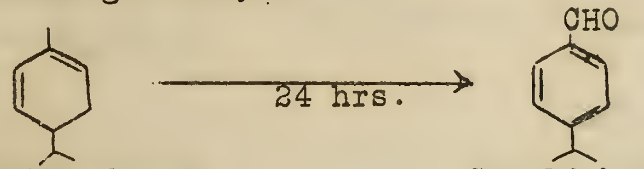
25. $CH{\equiv}CH \xrightarrow{40-50^\circ} CHOCHO$ 6 per cent

Asahina and Ishidate oxidized camphor to keto-camphor.

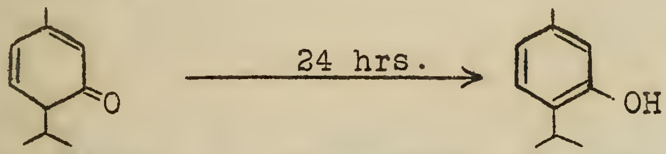
26. 

Here there is a side reaction in which the methyl group is oxidized instead of the methylene group. Another example of this is the

oxidation of phellandrene which Schwenk and Borgwordt found to give the corresponding aldehyde.

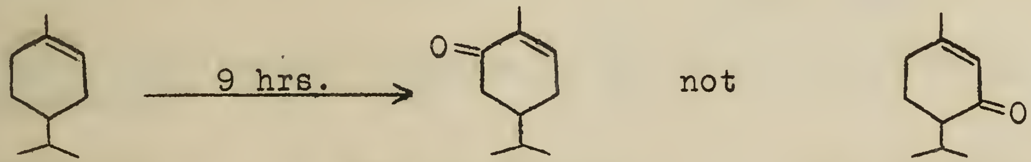
27. 

α-Phellandrene Cumaldehyde

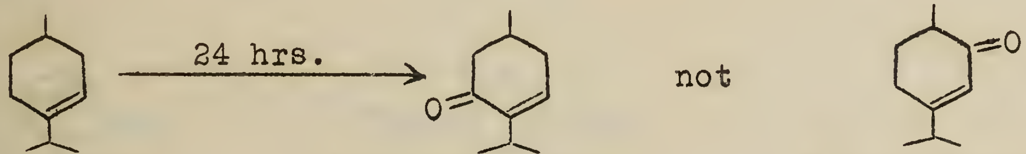
28. 

Piperitone Thymol

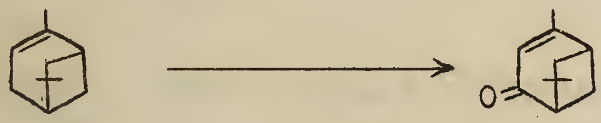
In these last two reactions, the selenium dioxide has also acted as a dehydrating agent. These same investigators found that when the terpenes were oxidized by selenium dioxide the CO group was always on the opposite side of the side chain from the double bond. For example:

29. 

Δ-1-Menthene Δ-1-Menthenone-6-carvotanacetone Δ-1-Menthone-3

30. 

Δ-3-Menthene Δ-3-Menthenone-5 Δ-3-Menthenone-2

31. 

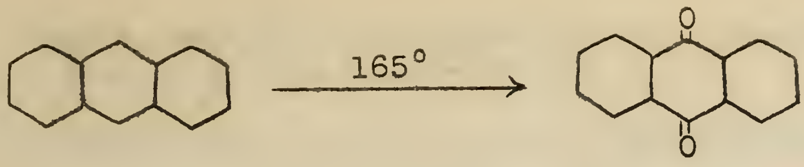
α-Pinene Verbenone

Postowski studied unsaturated compounds which had no adjacent methylenes and supplemented the work of Riley and Schwenk.

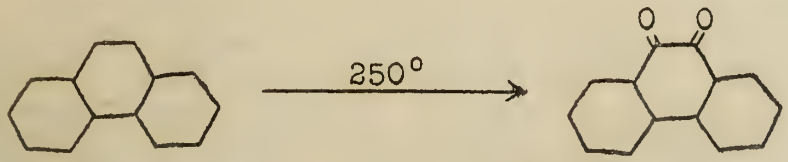
32. $C_6H_5-C\equiv C-C_6H_5 \longrightarrow C_6H_5COCOC_6H_5$ 35 per cent

33. $C_6H_5CH=CHC_6H_5 \longrightarrow C_6H_5COCOC_6H_5$ 17 per cent

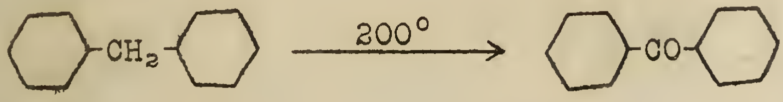
He also experimented with condensed polynuclear hydrocarbons and acetic anhydride.

34. 

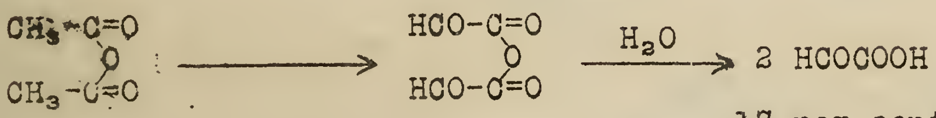
85 per cent

35. 

3 per cent

36. 

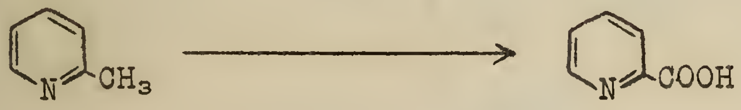
87 per cent

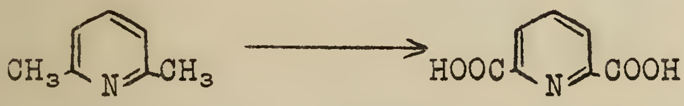
37. 

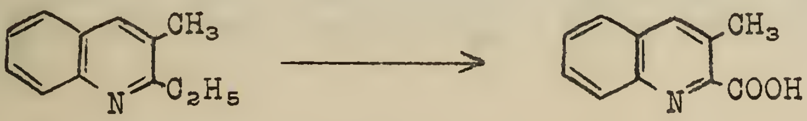
$(CH_3-C{=}O)_2O \rightarrow (HCO-C{=}O)_2O \xrightarrow{H_2O} 2\ HCOCOOH$

17 per cent

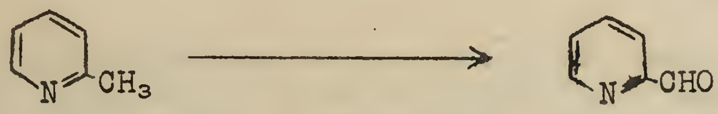
Henze applied the oxidation of the methyl group to the heterocyclic rings.

38. 

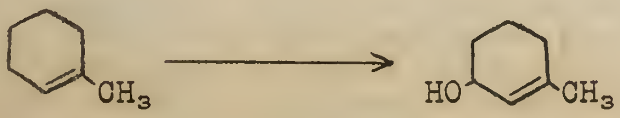
39. 

40. 

These are the only known examples of oxidation to the acids with selenium dioxide.

41. 

Oxidation of the methyl group may also give the corresponding alcohol.

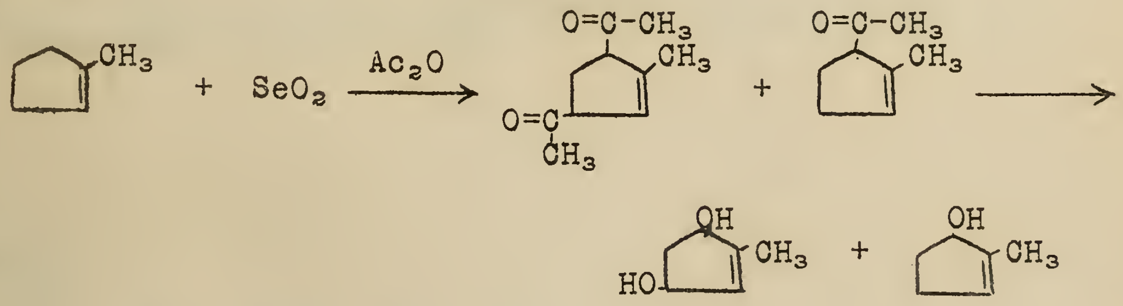
42. 

Müller showed that acetonylacetone formed an intermediate hydroxy compound which was further oxidized.

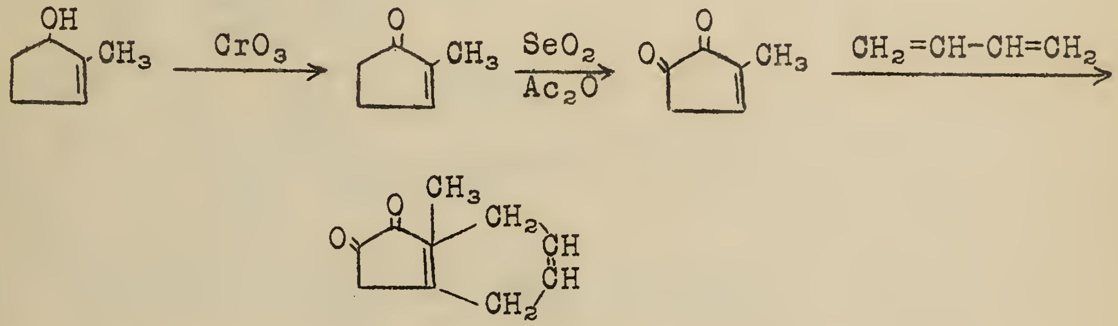
43. $CH_3COCH_2COCH_3 \longrightarrow CH_3COCOCOCH_3$

Last year it was thought that through selenium dioxide oxidation we were close to preparing hydrogenated polycyclic ring systems such as cyclopentanoperhydroxyphenanthrene, of which the sterols, bile acids, sex hormones, Vitamin D, plant heart poisons and toad poisons are derivatives. Methyl cyclopentadione was prepared from methyl cyclopentene. This ketone was active enough to react with butadiene.

44.

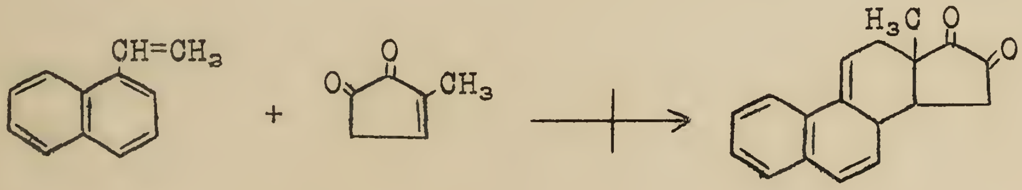


45.



Attempts to condense cyclopentadione, however, with a suitable diene to form a tetracyclic ring system containing a five-membered ring and a quaternary methyl group have not yet been successful.

46.



The difficulties in preparing the sterol nucleus are caused by the quaternary aliphatic group, the variety of possible isomers due to the number of asymmetric carbon atoms and cis-trans forms, and the amount and position of unsaturation.

Summary.-- Selenium dioxide oxidizes a variety of organic compounds, giving, in many instances, excellent yields of compounds difficult to prepare by other methods. In the majority of cases studied, the organic compounds contain, closely associated with a

negative group, a methylene group which is oxidized to carbonyl by selenium dioxide; e.g. aldehydes and ketones give 1,2-ketoaldehydes and 1,2-diketones respectively. Malonic ester gives mesoxalic ester. Acetoacetic ester gives α,β-di-ketobutyric ester. Besides this extensive type of reaction, examples are known in which selenium dioxide behaves differently; e.g. the group -CH=CH- in ethylene and propylene is oxidized to -COCO-. α-Pinene is oxidized to verbenone, involving the conversion

$$>C=CH-CH_2-CH< \longrightarrow >C=CH-CO-CH<$$

The simple aliphatic aliphatic alcohols give alkyl glyoxals and succinic ester gives fumaric ester.

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